COMMUNITY FUNCTIONING AND COGNITIVE PERFORMANCE IN SCHIZOPHRENIA: THE NATURE OF THE RELATIONSHIP

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Submitted to the Graduate Faculty of the

Kenneth P. Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science in Clinical Psychology

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

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Although cognition is one of the most important predictors of community functioning in schizophrenia, little is known about the causes of this relationship. This study is the first to our knowledge to examine the extent to which this correlation is genetically and/or environmentally mediated and its degree of specificity to schizophrenia. Six hundred and thirty-six participants from 43 multigenerational families with at least two schizophrenia relatives and 135 unrelated controls underwent diagnostic interview and functioning assessment along with the Penn Computerized Neurocognitive Battery, Trail Making Test and California Verbal Learning Test. Exploratory factor analyses yielded one general cognition factor and one functioning factor while a social cognition factor was comprised of the average of two tasks. SOLAR (Sequential Oligogenic Linkage Analysis Routines) (Almasy & Blangero, 1998) was used to conduct family-based analyses quantifying genetic and environmental effects on the cognition-functioning correlation. As expected, among the 103 relatives with schizophrenia, there was considerable variation in functioning and cognitive performance and a significant correlation between the two (R_P=0.335, p=0.005). Shared genetic effects were significant contributors to this relationship (R_G=0.956, p<0.001) whereas idiosyncratic experiences were not. In contrast, shared genetic effects were not significant among relatives with major depression, substance abuse or no psychopathology. Furthermore, functioning in schizophrenia was not significantly predicted by cognition in relatives from other diagnostic groups. Across all analyses, the contributions of social cognition to functioning were similar to and fully accounted for by general cognition. The cognition-functioning correlation in schizophrenia is largely attributable to genetic factors specific to the disorder that also encompass genetic effects on the association between social cognition and functioning. These findings provide a foundation from which heritable factors contributing to functioning in schizophrenia can be differentiated from those contributing to functioning in psychiatric disorders in general, which suggest that investigations of specific genetic variants contributing to this association are warranted.

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1.0 INTRODUCTION

Schizophrenia is a devastating disorder often characterized by hallucinations, delusions, and disordered thoughts during acute phases of illness, as well as deficits in normal emotions and behaviors, such as flattened affect, lack of motivation, and lack of ability to form relationships, during periods of remission. Striking approximately one in every hundred individuals, it is one of the leading causes of disability worldwide (Murray & Lopez, 1997). The ramifications of functional disability in schizophrenia are enormous. Estimates of the economic burden of schizophrenia in the United States for the year 2002 totaled $63 billion; the largest contributor to the indirect cost was attributed to unemployment, which accounted for more than a third of this total cost (Wu et al., 2005). As such, difficulties in functioning, which comprises independent living as well as social and occupational functioning, form a largely unmet need in individuals affected with schizophrenia.

Results from longitudinal and cross-sectional studies suggest that patterns of deficits in functioning often appear before the emergence of psychotic symptoms and persist in subsequent years (Agerbo, Byrne, Eaton, & Mortensen, 2004; Racenstein et al., 2002). Moreover, deterioration from premorbid functioning is more common than improvement from functional disability (Wiersma et al., 2000). While many individuals with schizophrenia experience broad deficits across domains of functioning, there is substantial variability in the degree of functional impairment (Palmer et al., 2002).

In attempting to explain these individual differences, cognition has emerged as one of the most important predictors of functioning in schizophrenia. In general, cognitive deficits have been consistently identified as a core feature of the diagnosis (Dickinson, Ragland, Gold, & Gur, 2008). Indeed, in forming the basis for our current conceptualization of schizophrenia, Kraepelin (Kraepelin, 1919) described cognitive dysfunction as a core feature of the disorder, which he termed ‘dementia praecox’, or premature dementia. While individuals with schizophrenia on

average reliably demonstrate deficits across cognitive domains approximately one standard deviation below that of unaffected individuals (Gold & Dickinson, 2013), there are also striking individual differences in cognitive abilities, ranging from deficits akin to those found in dementia to performance that is not differentiable from that of healthy controls (Joyce & Roiser, 2007). Unlike positive symptoms, cognitive deficits are relatively stable across phases of illness and have been found in first episode patients (Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999) as well as relatives of individuals with schizophrenia (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004).

Overall, cognition has been found to be a more important predictor of functioning than positive or negative symptoms, yielding a correlation of 0.25 largely independent of illness chronicity, inpatient status, age and sex (Fett et al., 2011). On the basis of replicable findings linking cognition with functioning in schizophrenia, there has been a surge of interest in developing cognitive remediation therapies with the hope of improving functional outcomes. A recent meta-analysis including over 2,000 participants found that cognitive remediation therapies show medium effect sizes for improvements in cognitive abilities, as well as small-to-medium effect sizes for improvements in functioning (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Furthermore, patients who underwent cognitive remediation reported greater improvements in measures of social adjustment such as work readiness than patients who participated in a supportive therapy that did not target cognitive deficits (Hogarty et al., 2004). The efficacy of cognitive training beyond therapy or rehabilitation alone points to the importance of cognitive abilities in the activities of daily living.

In view of the large body of literature examining the association between cognitive performance and functioning in schizophrenia, there is an astonishing dearth of research addressing the underlying causes of this association. In particular, no studies thus far have examined whether this association may be more attributable to shared genetic effects or environmental experience. The extent to which genetic liability for cognitive deficits and genetic liability for functioning overlap in schizophrenia has remained completely unexplored. Thus, the aim of the current study is to examine the etiology and specificity of the cognition-functioning correlation in schizophrenia.

1.1 FUNCTIONING AND COGNITION IN SCHIZOPHRENIA

In a literature currently spanning over 200 peer-reviewed articles, there is strong evidence of a replicable, medium effect size for a cognition-functioning correlation in schizophrenia, suggesting that many individuals with the diagnosis struggle to function in their communities and also have problems with their cognitive abilities (Fett et al., 2011). In order to better understand this association and provide a basis for examining its etiology and specificity, it is first important to examine the various approaches to conceptualizing the two constructs, the issues and the findings surrounding how specific cognitive domains may relate to functioning, and the specificity of this association to schizophrenia compared to other diagnoses.

1.1.1 Functional Outcomes

The most recent review of psychosocial outcome measures in schizophrenia patients highlights the lack of consensus in defining appropriate standards for levels of functioning and for terminology (Figueira & Brissos, 2011). Overlapping concepts include social functioning, social adjustment, social adaptation, social competence, and functioning, the last of which will be used in this paper. Broadly speaking, the measurement of functioning has been approached in two ways: direct measures assessing an individual's actual functioning in the community and proxy measures assessing what an individual may be capable of accomplishing. The former draws largely upon clinical interviews and questionnaires of real-world behaviors while the latter includes performance-based assessments of functional capacity in laboratory settings and skill acquisition in rehabilitation settings. Although a similar pattern of positive results arises from both approaches to measuring functioning, proxy measures generally show stronger associations with nonsocial cognition than do direct measures (Fett et al., 2011). Unlike direct measures, proxy measures are thought to assess optimal functioning as they are unconstrained by environmental factors that may impact functioning such as socioeconomic status (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006). Despite such potential advantages, proxy measures ultimately remain analogues for real-world functioning. As such, direct measures of functioning will be emphasized here.

Assessments of psychosocial outcomes often encompass many domains (Figueira & Brissos, 2011). Beyond those encompassing behavior, symptoms, health and treatment, or quality of life, there are three domains that may be most relevant to real-world functioning: living situation, occupational and educational situation and relationships. Living situation refers to an individual's ability to take care of themselves with minimal assistance, such as managing finances and planning leisure activities. Occupational and educational situation is often assessed by the duration and responsibilities of gainful employment or academic study. Relationships comprise interpersonal relationships within and outside the family, and can include measures of household integration, social activities and communication.

1.1.2 General, Specific and Social Cognition

In understanding how cognition may relate to functioning, the question naturally arises of whether there are specific cognitive domains that are more associated with functioning than others. If functioning is associated with greater deficits for certain cognitive processes, this may designate such deficits as more critical targets for improving functional outcomes. Alternatively, perhaps more general cognitive deficits are most associated with functioning. In the most recent meta-analysis, overall cognition was significantly correlated with general functioning (r = 0.25) (Fett et al., 2011). Across specific nonsocial cognitive tasks, only verbal fluency may be more highly correlated with functioning (r = 0.32).

Beyond general cognition, social cognition has been proposed to be a more proximal predictor of functioning than general cognition. In a recent review, all ten studies examining general cognition as a predictor of functioning provided evidence for the mediating role of social cognition, with indirect effect sizes ranging from 0.14 to 0.28 depending on the domain of social cognition (Schmidt, Mueller, & Roder, 2011). Thus, the results suggest that there is a small to medium effect of social cognition in mediating general cognition and functioning, with certain social cognitive domains being more tightly linked to these two constructs compared to other domains.

Overall, general cognition is robustly associated with functioning in schizophrenia and comprises the vast majority of the variance in functioning accounted for by specific cognitive

domains. While social cognition shares predictive power for functioning with general cognition, it also has been found to predict functioning independently of general cognition.

1.1.3 Specificity of the Cognition-Functioning Correlation to Schizophrenia

While few studies in this area have included direct comparisons of the cognition/ functioning association in schizophrenia with other psychiatric disorders, those that have suggest that cognition is more highly associated with functioning in schizophrenia compared to bipolar disorder (Jabben, Arts, van Os, & Krabbendam, 2010; Martínez-Arán et al., 2002) and that the relative importance of certain cognitive domains for functioning may differ between these disorders (Laes & Sponheim, 2006; Tabares-Seisdedos et al., 2008). Beyond bipolar disorder as a psychiatric comparison for schizophrenia, there has been a lack of comparisons with more prevalent psychiatric disorders. To this end, the current study compares the cognition-functioning correlation across schizophrenia, major depression and substance abuse.

1.1.4 Origins of the Cognition-Functioning Correlation in Schizophrenia

Given that schizophrenia is a highly heritable disorder, with approximately 65% or more of liability to schizophrenia attributable to genetic liability (Lichtenstein et al., 2009), it is surprising that functional deficits have remained largely unexplored from a genetic perspective. The only extant study of the familiality of cognition in schizophrenia found that performance on some specific cognitive measures was correlated within concordant relatives (Hoff et al., 2005). Similarly, all but one of the few studies examining the genetic effects on functioning establish the familiality of composite and global measures of functioning in schizophrenia (Burke, Murphy, Bray, Walsh, & Kendler, 1996; Cardno et al., 1998; Deshpande et al., 2004; Kendler et al., 1997; McGrath et al., 2009; Vassos et al., 2008), while genetic effects on specific functioning measures are more mixed (Bhatia, Franzos, Wood, Nimgaonkar, & Deshpande, 2004; Deshpande et al., 2004; Wickham et al., 2002).

Although there is research in schizophrenia to suggest that variation in cognition is affected by genetic influences and some initial evidence that functioning may be heritable, the current study is the first to examine the extent to which phenotypic relationships between

cognitive abilities and functioning outcomes are mediated by genetic and environmental factors. This study also aims to explore the nature of these relationships by examining differences between general and social cognition in predicting functioning. Furthermore, this study will address the specificity of the cognition-functioning correlation by comparing these relationships across multiple diagnostic categories, providing a basis from which we can begin to parse the contribution of heritable factors to functioning in schizophrenia from those that contribute more broadly to functioning in psychiatric disorders in general. The results of this study may inform future research into the specificity of pathways contributing to functional outcomes.

To improve our understanding of the genetic liability for the association between cognition and functioning, we draw upon a multiplex, multigenerational family sample. This ascertainment strategy has advantages over the traditional sibpair design, as the power to detect genetic liability for traits increases with family size and since both functioning and cognition can be measured in relatives who are not affected with schizophrenia, fewer pedigrees are necessary. In addition, the sample does not exclude relatives of probands who meet diagnostic criteria for disorders other than schizophrenia, rendering them especially suitable for addressing the specificity of this association to schizophrenia relative to other diagnoses.

1.2 QUESTIONS & HYPOTHESES

The primary aim of this study was to determine the relative influence and diagnostic specificity of genetic and environmental factors on the cognition-functioning correlation in schizophrenia. Given that composite measures of cognitive performance have been more consistently predictive of functioning than specific measures, this approach was be emphasized, and similarly, no specific hypotheses were made regarding the contribution of cognition towards a particular functional outcome. The questions that this study aimed to address are:

1) Do participants with schizophrenia demonstrate significant mean deficits in cognition and functioning compared to participants with major depression, substance abuse, or no diagnosis participants? Given that previous studies have established that individuals with schizophrenia demonstrate deficits in functioning and cognition that are more severe than

those of patients affected with other disorders and those of the general population, this will provide support for the generalizability of our results.

2) What is the degree of individual differences in cognition and functioning in schizophrenia?
3) Within individuals, what are the phenotypic correlations between cognition and functioning separately among schizophrenia, major depression, substance abuse, or no diagnosis relatives? We hypothesize that this association will be significant in schizophrenia and perhaps larger than in other diagnostic groups.
4) Are individual differences in cognition heritable in schizophrenia and in other diagnoses in this sample? Similarly, are individual differences in functioning heritable in schizophrenia and in other diagnoses in this sample? We hypothesize that both cognition and functioning will be heritable in schizophrenia and perhaps to a larger extent than in other diagnoses.
5) Among relatives concordant for schizophrenia, what are the genetic and environmental correlations between cognition and functioning? We hypothesize that there will be a significant genetic correlation underlying the cognition-functioning phenotypic correlation in schizophrenia. This is the primary question of the study and has not been investigated to date.
6) Across relatives with different diagnoses, what are the genetic and environmental correlations between cognition and functioning? Are these genetic correlations unique to schizophrenia or shared with other psychopathology? As noted above, we hypothesize that the cognition-functioning genetic correlation among schizophrenia relatives will be significant. In contrast, we hypothesize the correlation between functioning in schizophrenia and cognition in relatives with major depression, substance abuse or no diagnosis to be nonsignificant. This would suggest that the cognition-functioning genetic correlation is to some degree specific to schizophrenia. However, if the correlations are significant across diagnoses in relatives, this would suggest that the relationship between functioning and cognition is not specific to schizophrenia and may be attributable to a more general cognition-functioning genetic correlation, either within psychopathology in general, or perhaps also within the general population.
7) As an exploratory question, if this cognition-functioning genetic correlation is specific to schizophrenia relative to other diagnoses, do positive symptoms or negative symptoms mediate this correlation? Based on the results of a recent meta-analysis (Ventura,

Hellemann, Thames, Koellner, & Nuechterlein, 2009), we hypothesize that negative symptoms will mediate this association, whereas positive symptoms will not. This would suggest that the uniqueness of this correlation in schizophrenia may be due to processes related to negative symptoms.

2.0 METHODS

2.1 PARTICIPANTS

Probands and their relatives were recruited by the University of Pittsburgh (PITT) or the University of Pennsylvania (PENN) through mental health and consumer organizations throughout Pennsylvania, New Jersey, Delaware, Ohio, West Virginia, Kentucky, Michigan and Indiana. Probands were included if they had a diagnosis of schizophrenia, were of European-American descent, at least 18 years old and competent to provide informed consent. Furthermore, probands also had to have at least one first-degree relative with a diagnosis of schizophrenia or schizoaffective disorder – depressed type and a multigenerational family with ten or more first- and second-degree relatives. Probands were excluded if they did not provide consent to contact their relatives, were not proficient in English or their diagnosis was possibly due to substance use, prescription medications, or medical conditions. Inclusion criteria for relatives comprised being at least 15 years old and willing to provide consent, while exclusion criteria included lack of proficiency in English, or a brain injury or disorder that would interfere with interpretation of cognitive measures.

European-American individuals aged 18-84 were recruited for inclusion in the control group. Screening excluded controls if they or a first-degree relative had been diagnosed with a schizophrenia spectrum disorder or other psychotic disorder, were taking antipsychotic medications, or if they had experienced any of the following: recent exacerbation of non-psychotic psychiatric symptoms (e.g., psychiatric hospitalization or a dose increase of psychiatric medication in the past month), electroconvulsive therapy in the past six months, treatment for substance abuse in the past six months, medical condition that could produce psychiatric symptoms or cognitive deficits (e.g., Alzheimer's disorder), history of head injury resulting in cognitive changes, or sensory or physical impairments that could interfere with completion of

study measures. Controls recruited at PITT were attempted to be group matched to the relatives based on average age and sex. Potential control individuals residing in the regions from which most probands and their relatives had been recruited were initially contacted through random digit dialing and underwent a phone screen. Controls at PENN were recruited through advertisements and word of mouth and were administered a screening interview. A second group of PENN controls was included who had undergone data collection prior to this study. These controls were administered the same interview as the other PENN control participants to screen for psychopathology and completed the same study procedures.

Using protocols approved by the Institutional Review Boards at PITT, PENN and the Texas Biomedical Research Institute, participants provided written informed consent after the study procedures had been fully explained; those who were under the age of 18 provided assent and their parents provided consent.

2.2 PROCEDURES

2.2.1 Diagnostic Assessment

Clinical evaluation utilized the Diagnostic Interview for Genetic Studies, version 2.0 (DIGS) (Nurnberger et al., 1994), the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992), and a review of medical records if available. Assessment was conducted in person, or rarely over the phone if an in-person interview was infeasible, by trained interviewers who were not blind to the status (proband, relative, or control) of the participants. At each site, interrater reliability among investigators and interviewers was tested at regular intervals using videotaped interviews. Interviewers from each site reviewed videotaped DIGS evaluations from the other site, ensuring that kappa values for exchanged tapes were maintained at or above 0.8. The two teams met twice a year for further diagnostic and reliability training. At least two investigators (licensed psychologists and psychiatrists) who had not evaluated the individual reviewed each case independently and provided DSM-IV multiaxial lifetime diagnoses, with differences being resolved by consensus. In addition, complex cases were discussed between sites.

2.2.2 Functioning

Four objective measures of current functioning were selected from the DIGS and coded as follows (high scores reflect better functioning).

Current Marital Status. As a measure of social functioning, participants were grouped into three categories: 1) never married; 2) separated or divorced; 3) married or widowed.

Current Living Situation. As a measure of independent living, participants were grouped into five categories: 1) in a residential treatment facility; 2) in home of relatives; 3) alone or with roommates (i.e. non-lineal relatives or friends); 4) with unmarried partner for at least one year; 5) in own home with spouse and/or children.

Current Occupational Status. As a measure of work functioning, Hollingshead's original 22 employment categories were re-categorized to yield an ordered ranking (Hollingshead, 1975). The modified DIGS coding scheme of employment was: 1) unemployed (under the age of 65) ; 2) disabled; 3) homemaker; 4) operators, fabricators, and laborers; 5) farming, forestry fishing, production, craft and repair; 6) service; 7) full time student; 8) technical, sales, and administrative support; 9) professional; 10) managerial positions. For individuals who were retired (unemployed and over the age of 65), the most responsible job they had ever held was coded as their occupational status according to the ordered ranking.

Current Global Functioning. The Global Assessment of Functioning Scale (GAF) (Endicott, Spitzer, Fleiss, & Cohen, 1976)gauges lowest level of functioning during the past month on a scale of 1 to 100, with 1 representing the most impairment and 100 representing the most adaptive.

2.2.3 Cognition

Participants were administered a computerized neurocognitive battery that has been utilized in both healthy and patient samples (R. C. Gur, Ragland, Moberg, Bilker, et al., 2001; R. C. Gur, Ragland, Moberg, Turner, et al., 2001). The battery took approximately 60 minutes to complete and tasks were administered in a fixed order by research assistants using laptop computers. The tasks included training modules and had automated scoring to ensure reliability of results. Two performance indexes were recorded for each measure: accuracy (number of correct responses)

and reaction time (median reaction time for correct responses). Raw scores were converted to z-scores using the mean and standard deviation of controls, and efficiency scores (which were the only scores used) were calculated by subtracting standardized reaction time from the standardized accuracy. Thus, higher efficiency scores reflect both better accuracy and faster performance.

The battery assessed the following domains (as previously reported in Gur et al., 2007) from two broad categories, general cognition and emotion perception (the latter being a domain of social cognition):

2.2.3.1 General Cognition

Abstraction and Mental Flexibility. The Penn Conditional Exclusion Test (Kurtz, Ragland, Moberg, & Gur, 2004) simultaneously presents four objects for each trial; the participant then selects the object that does not belong with the other three based on one of three sorting heuristics. Feedback guides the identification of changes in sorting heuristics (time: 12 minutes).

Attention. The Penn Continuous Performance Test (Kurtz, Ragland, Bilker, Gur, & Gur, 2001) uses a continuous performance test paradigm in which the participant responds to seven-segment displays whenever they form a digit. There is no working memory load since the stimulus is presented for the full duration of a trial (time: 8 minutes).

Verbal Memory. The Penn Word Memory Test (Gur et al., 1993) presents 20 target words followed by an immediate recognition trial with the targets and 20 distractors words randomly interspersed, and a delayed recognition trial 20 minutes later. The distractor words are chosen to match target words on frequency, length, concreteness, and low imageability using Paivio's norms. (time: 4 minutes).

Spatial Memory. The Visual Object Learning Test (Glahn, Gur, Ragland, Censits, & Gur, 1997) presents 20 Euclidean shapes followed by an immediate recognition trial with random foils and a delayed recognition trial 20 minutes later. (time: 4 minutes).

Spatial Processing. Judgment of Line Orientation (Benton, 1975) is a computer adaptation of Benton's test, in which participants are presented two lines at an angle and select the corresponding lines on a simultaneously presented array (time: 6 minutes).

Sensorimotor Dexterity. The participant uses a mouse to click on squares appearing at different locations on the computer screen; the squares become progressively smaller in later trials (Gur, Ragland, Moberg, Turner, et al., 2001) (time: 2 minutes).

Participants also completed three additional pencil and paper tasks:

Trail Making Task. Attention and processing speed were assessed using both versions (A & B) of the Trail Making Task (Reitan, 1958). In Part A, participants are instructed to connect a set of 25 dots each containing a number in sequential order as quickly as possible. In Part B, participants connect dots that alternate between numbers and letters. For both parts, the time to completion (in seconds) was multiplied by -1. Thus, increasing scores reflect faster, better performance.

California Verbal Learning Test (CVLT) (Delis, 1987). Participants are read aloud a list of sixteen common words belonging in four categories, then are asked to recall (without regard for order) as many of these items as possible after each of five trials. The number of words correctly recalled on the fifth trial was used as a measure of verbal memory.

2.2.3.2 Emotion Perception

Face Memory. The Penn Face Memory Test (Gur et al., 1993) randomly presents 20 digitized faces followed by an immediate recognition trial with 20 randomly presented foils and a delayed recognition trial 20 minutes later (time: 4 minutes).

Emotion Processing. The Emotion Intensity Discrimination Test (Gur et al., 2006) contains 40 trials displaying two faces of the same individual. The two faces show the same emotion (happy or sad) at different intensities, and the participant is asked to select the more intense expression. Sets were balanced for gender, age, and ethnicity (time: 5 minutes).

2.2.3.3 Verbal Intelligence

Wide Range Achievement Test (Wilkinson, 1993) The WRAT Word Reading subtest (Blue Form) was used as a global estimate of verbal IQ (age-based norms).

2.2.4 Negative and Positive Symptoms

The Scale for the Assessment of Negative Symptoms (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (Andreasen, 1984) are designed to assess severity of negative symptoms and positive symptoms, respectively. Interviewers used 6-point Likert scales to rate symptom severity based on the last 30 days with response options ranging from 0 (none) to 5 (severe). Each subscale contains a number of items addressing specific symptoms as well as a global rating that summarizes overall symptom severity within the domain. The global ratings were used to create a summary score, since the global ratings for each domain in the SANS and SAPS may represent more clinically sensitive indexes than the individual items in the same domains (Andreasen, 1982), and global summary scores tend to be more reliable than the individual symptom ratings (Norman, Malla, Cortese, & Diaz, 1996). From the SANS, a summary score of negative symptoms was made by averaging the completed global ratings of affective flattening, alogia/poverty of speech, avolition/apathy, anhedonia/ asociality, and attention. Similarly, from the SAPS, a summary score of positive symptoms was made by averaging the completed global ratings of hallucinations, delusions, bizarre behavior, and positive formal thought disorder.

3.0 RESULTS

3.1 SAMPLE

The initial total sample included 773 participants with diagnostic information who had at least one of the four Functioning variables or at least one of the 11 Cognition variables, for a total of 638 pedigree members and 135 unrelated controls. Within the 638 pedigree members, 105 participants affected with Schizophrenia or Schizoaffective Disorder and 533 unaffected participants were drawn from 43 multiplex, multigenerational families. The size of each enrolled family is summarized in Appendix Table 1.

The eleven cognitive variables included in the analysis were the eight CNB tasks and three pencil and paper tasks: Trails A, Trails B and CVLT. Only participants who had data for half or more of the cognitive variables or more than half of the Functioning variables were included in the final analysis sample, as participant characteristics may have contributed to the lack of data for the majority of the variables and thus presented a potential bias. Incomplete data were attributable to computer malfunction during the CNB tasks, participants' inadequate comprehension of the task instructions, participants' refusal to complete the tasks, problems with eliciting or clarifying information from participants regarding their current functioning, or data deemed invalid due to deviations in the participants' behaviors or the testing conditions.

More than 60% of participants had complete data for Cognition and Functioning variables (see Appendix Table 2). Only two unrelated pedigree members, both diagnosed with schizophrenia, were excluded from the final sample because they had fewer than half of both Cognition and Functioning variables (having data for one Functioning variable and five Cognition variables). Eight pedigree members who had Functioning data had invalid CNB data (these included four individuals in the Schizophrenia group, one individual in the Substance abuse group, two individuals in the No Diagnosis group, and one individual in the Other group).

Since their cognitive testing differed from the rest of the sample, their data on the pencil-and-paper tasks (Trails A, Trails B and CVLT) were also excluded. Thus the final sample for analysis consisted for 771 participants, including 636 pedigree members and 135 controls.

3.1.1 Diagnostic Composition

Participants were classified into five hierarchical, mutually exclusive diagnostic groups (see Table 1). The number of pedigree members in each diagnostic group per family is summarized in Appendix Table 3. Of the 103 pedigree members in the Schizophrenia group, co-occurring diagnoses included substance abuse (*N*=28), depressive disorder, NOS (*N*=9), both substance abuse and depressive disorder, NOS (*N*=2), and mood disorder, NOS (*N*=1). Of the 82 pedigree members in the Major Depression group, co-occurring diagnoses included dysthymia (*N*=2), personality disorder not otherwise specified (NOS) (*N*=2), oppositional defiant disorder (*N*=1), bulimia nervosa (*N*=1), and anxiety disorder, NOS (*N*=1). Other than two participants who had personality disorder NOS and one with conduct disorder, none of the 57 pedigree members in the Substance abuse group had any other psychopathology, although many met criteria for substance use or dependence for more than one substance. Forty-five pedigree members having both major depression and substance abuse were classified in the Other group to avoid overlap in analyses. Of these 45 individuals, 29 had substance abuse and major depression (27 had major depression as the primary diagnosis), 11 had substance abuse and depressive disorder, NOS, four had substance abuse and mood disorder, NOS, and one had substance abuse and alcohol-induced mood disorder. Twenty-one individuals with psychotic disorder, delusional disorder or mood disorder (major depressive or bipolar) with psychotic features, 22 individuals with Cluster A personality disorder, including schizotypal, schizoid and paranoid personality disorder, and 45 participants with miscellaneous diagnoses were also placed in the Other group. In terms of cognitive disorders, one affected pedigree member received a comorbid diagnosis of mental retardation, having a standardized WRAT score of 43, and two pedigree members received a diagnosis of dementia; all three were placed in the Other group.

Of the Control group, 21 individuals were diagnosed with major depression and nine were diagnosed with substance abuse. Three control participants received concomitant diagnoses of major depression and substance abuse, four received a diagnosis of adjustment

disorder, two received a diagnosis of depressive disorder, NOS, and one reported a history of sexual abuse.

Table 1. Mutually exclusive diagnostic hierarchy for pedigree members and control participants.

Diagnosis	*Diagnostic Group*	*Pedigree Members*	*Controls*
Schizophrenia or schizoaffective disorder	SC	103	-
Major depression	MDD	82	21
Substance abuse	SUD	57	9
Other psychiatric diagnosis	Other	136	10
No psychiatric diagnosis	ND	258	95
Total		636	135

3.1.2 Demographic Characteristics across Groups

Demographic comparisons across relevant pedigree diagnostic groups and the total control group are provided in Table 2, given that the factor analyses were performed on the overall sample including individuals with psychiatric diagnoses other than the main diagnoses of interest (Schizophrenia, Major Depression, Substance Abuse and No Diagnosis). Overall chi-square tests indicated significant differences for recruitment site and sex, and one-way ANOVAs among diagnostic groups for age, education and WRAT were also all significant.

Controls had relatively more participants than the pedigree diagnostic groups recruited from PITT. A greater proportion of females were recruited in the Major Depression and Control groups, while the Schizophrenia, No Diagnosis and Other Diagnosis groups had a more equal balance of males and females, followed by the Substance abuse group, which had proportionately more males than all other groups. Controls were also significantly older and attained more years of education than all pedigree groups except for Major Depression, while individuals in the Major depression and No Diagnosis groups had comparable years of education. The Control group also had similar WRAT scores to the Major Depression and No Diagnosis

groups, all of which had higher WRAT scores than Schizophrenia, Substance Abuse and Other Diagnosis groups.

Table 2. Demographic comparisons among diagnostic groups in the total sample.[1]

Diagnostic Group	*N*	*Site* *% Pitt (N)*	*Sex* *% Male (N)*	*Age* *Mean (SD)*	*Education** *Mean (SD)*	*WRAT*** *Mean (SD)*
Pedigree Members	636	42.6% (271)	48.3% (307)	45.17 (17.36)	13.15 (2.93)	98.95 (14.53)
SC	103	38.8% (40) [a]	58.3% (60) [a]	46.63 [a] (12.54)	12.44 (2.72) [a]	91.95 (15.75) [a]
MDD	82	47.6% (39) [ab]	23.2% (19) [b]	44.73 [a] (14.71)	14.20 (2.83) [bc]	102.86 (11.61) [b]
SUD	57	35.1% (20) [a]	87.7% (50) [c]	43.77 [a] (16.08)	12.68 (2.96) [a]	94.86 (12.13) [a]
Other	136	41.9% (57) [a]	47.8% (65) [ad]	42.51 [a] (16.83)	12.65 (2.90) [a]	95.75 (16.10) [a]
ND	258	44.6% (115) [a]	42.5% (107) [ad]	46.42 [a] (20.06)	13.48 (2.93) [ab]	102.80 (13.00) [b]
Controls	135	65.2% (88) [b]	37.0% (50) [bd]	54.71 [b] (16.75)	14.92 (2.43) [c]	108.34 (8.43) [b]
Statistic		25.93	71.88	8.46[×]	14.12	25.52[×]
df		5	5	5, 272	5, 768	5, 222
p-value		0.0001	0.0001	0.0001	0.0001	0.0001

3.1.3 Outliers

Cases with Functioning or Cognition scores deviating more than three standard deviations from the next ranked case were Winsorized (assigned the next score closest to the mean). This

[1] Results of one-way ANOVAs are reported with the F-statistic or the Welch statistic, where appropriate, and results for site and sex are reported with the Pearson chi-square statistic. Given that all omnibus tests were significant at $p = 0.0001$, post-hoc Tukey's pairwise tests were conducted. Statistics sharing the same superscripts did not differ significantly ($p \leq 0.05$) from each other (i.e. were included in a homogeneous subset).
[*]Education data available for 98.5% of the controls ($N = 133$) and 100% of pedigree members. [**]WRAT: Wide Range Achievement Test (age-standardized value). WRAT data available for 84.6% of all pedigree members ($N = 538$) and 85.2% of controls ($N = 115$). [×] indicates significant difference across groups in homogeneity of variance; Welch's statistic reported instead of F-statistic

adjustment was made in one instance each for Verbal Memory, Spatial Memory and Trails A, and in two instances for Sensorimotor Dexterity.

3.2 DATA REDUCTION

3.2.1 Factor Analysis

Using the total pedigree and control sample, recruitment site, sex, and age were regressed onto all Functioning and Cognition variables in SPSS. Subsequently, the standardized residualized variables were subjected to exploratory factor analyses in Mplus (version 6.11) (Muthén & Muthén, 1998) using varimax rotation to derive factors for variables with missing data. Full information maximum likelihood (FIML) estimation yields unbiased parameter estimates in the presence of missing at random and missing not at random data. Rather than imputing values for component variables, Mplus estimates factor scores for individuals with missing data based on the individual's available data and the sample's covariance matrix. This rests upon the assumption that the covariance matrix among the tests is equivalent across varying degrees of genetic relatedness.

The Functioning factor was estimated using WLSMV (weighted least squares, mean- and variance-adjusted) adjustment due to the ordinal nature of the component items. Standardized factor scores for each participant were calculated for the Functioning variables and the General Cognition variables. The exploratory factor analyses yielded one-factor solutions for both Functioning and General Cognition; factor loadings and proportions of variance explained for each of the contributing variables are summarized in Table 3. All observed variables loaded significantly onto their respective factors at $p = 0.000$. Factor scores from these analyses were used in subsequent analyses. The factor loadings for each item were squared to derive the proportion of variance in the item accounted for by the factor; these proportions were averaged to calculate the variance in all items accounted for by the factor.

For the Functioning index, which on average accounted for 44.35% of the variance in the factor items, Marital Status and Living Situation had the highest item loadings. Using Horn's parallel analysis, a single factor emerged with an observed eigenvalue greater than the 95th

percentile of eigenvalues of factors derived from randomized data, as shown in Appendix Table 4a. Fit statistics for this index were mixed for goodness of model fit, $\chi^2(2) = 108.086$, $p = 0.000$; comparative fit index (CFI) = 0.871, root-mean-square error of approximation (RMSEA) estimate = 0.271, standardized root-mean-square residual (SRMR) = 0.086.

For the General Cognition index, which on average accounted for 49.99% of the variance in the factor items, all items had high loadings over 0.60 except Spatial Memory and Trails A. As with the Functioning index, a one-factor solution was indicated based on results of Horn's parallel analysis, as shown in Appendix Table 4b. Fit statistics for this index suggested good model fit, $\chi^2(27) = 158.061$, $p = 0.000$; CFI = 0.940, RMSEA estimate = 0.082, SRMR = 0.037.

Table 3. Factor loadings from separate exploratory factor analyses of functioning and cognition in the total pedigree and control sample.

	Factor Loadings	***% Variance of an item accounted for by factor***
Functioning		
Marital Status	0.795	63.20
Living Situation	0.918	84.27
Current Occupation	0.328	10.76
Global Functioning	0.438	19.18
General Cognition		
Abstraction and Mental Flexibility	0.707	49.98
Attention	0.682	46.51
Verbal Memory	0.715	51.12
Spatial Memory	0.578	33.41
Spatial Processing	0.925	85.56
Sensorimotor Dexterity	0.756	57.15
Trails A	0.414	17.14
Trails B	0.712	50.69
California Verbal Learning Test	0.764	58.37

3.2.2 Averaging Emotion Perception Tasks

After regressing recruitment site, sex, and age, the correlation between the standardized residualized efficiency scores for the two social cognitive tasks (Face Memory and Emotion

Processing) was significant ($r = 0.554$, $p = 0.000$). The two scores were then averaged to yield the Emotion Perception index. For sixteen cases, all of whom were pedigree members, the Emotional Processing score was missing, and only the Facial Memory score was included in the Emotion Perception index. Likewise, for three cases, two of whom were pedigree members, the Facial Memory score was missing, and only the Emotional Processing score was included in the Emotion Perception index. To examine Emotion Perception without the contribution of General Cognition, the residual score of Emotion Perception after regressing General Cognition was included in subsequent analyses in SPSS.

3.2.3 Demographic Correlations with Functioning and Cognition

Pearson correlations between demographics and Functioning and Cognition indexes and tests in the overall sample are displayed in Table 4. Indexes were factor scores based on scores adjusted for age, sex and site. Significance levels were adjusted for multiple comparisons using the Bonferroni correction ($p = 0.05/90 = 0.0006$).

The Functioning index was positively correlated with Education and WRAT performance. Individuals recruited from PITT had higher Functioning ratings on the GAF and there were no significant differences between sexes for any Functioning item. Increasing age was associated with better Marital Status and Living Situation ratings. Increased education was correlated with better Functioning for all Functioning variables. Similarly, WRAT performance was positively associated with all component items except for Marital Status.

The General Cognition and Emotion Perception indexes were moderately and positively correlated with Education and WRAT performance. Individuals recruited from PITT demonstrated higher performance on the Trails A and CVLT. Females also demonstrated higher performance on the Trails B and CVLT but worse performance on Spatial Processing. As expected, increasing age was negatively correlated with performance on all cognitive variables, while Education showed the opposite trend, showing better performance across all cognitive variables except Spatial Memory. Similarly, WRAT scores were positively correlated with better performance across all component items. After accounting for General Cognition, Emotion Perception was not significantly correlated with any demographic variable.

Table 4. Pearson correlations between demographic characteristics, functioning and cognition indexes and component items in the total pedigree and control sample. [2]

	Site	*Sex*	*Age*	*Education*	*WRAT*
Functioning Index	**0.016 (0.677)**	**-0.004 (0.905)**	**-0.004 (0.925)**	**0.198* (0.0001)**	**0.140* (0.001)**
Marital Status	0.067 (0.071)	0.048 (0.198)	0.511* (0.0001)	0.134* (0.0001)	0.096 (0.018)
Living Situation	0.097 (0.010)	0.094 (0.013)	0.347* (0.0001)	0.209* (0.0001)	0.144* (0.0001)
Current Occupation	0.032 (0.397)	0.057 (0.126)	0.014 (0.704)	0.406* (0.0001)	0.343* (0.0001)
Global Functioning	0.249* (0.0001)	0.131 (0.001)	0.023 (0.549)	0.277* (0.0001)	0.375* (0.0001)
General Cognition Index	**0.018 (0.627)**	**-0.005 (0.889)**	**-0.027 (0.464)**	**0.376* (0.0001)**	**0.512* (0.0001)**
Abstraction and Mental Flexibility	0.011 (0.777)	0.090 (0.019)	-0.433* (0.0001)	0.230* (0.0001)	0.351* (0.0001)
Attention	-0.073 (0.057)	0.059 (0.123)	-0.185* (0.0001)	0.247* (0.0001)	0.326* (0.0001)
Verbal Memory	0.002 (0.949)	0.128 (0.001)	-0.274* (0.0001)	0.255* (0.0001)	0.407* (0.0001)
Spatial Memory	-0.012 (0.755)	0.003 (0.929)	-0.406* (0.0001)	0.096 (0.012)	0.142* (0.0001)
Spatial Processing	0.006 (0.878)	-0.182* (0.0001)	-0.219* (0.0001)	0.301* (0.0001)	0.424* (0.0001)
Sensorimotor Dexterity	0.050 (0.189)	-0.006 (0.875)	-0.363* (0.0001)	0.186* (0.0001)	0.259* (0.0001)
Trails A	0.138* (0.0001)	0.070 (0.066)	-0.286* (0.0001)	0.136* (0.0001)	0.237* (0.0001)
Trails B	0.127 (0.001)	0.153* (0.0001)	-0.306* (0.0001)	0.196* (0.0001)	0.418* (0.0001)
California Verbal Learning Test	0.193* (0.0001)	0.218* (0.0001)	-0.210* (0.0001)	0.264* (0.0001)	0.367* (0.0001)
Emotion Perception Index	**0.010 (0.788)**	**0.004 (0.913)**	**-0.008 (0.834)**	**0.261* (0.0001)**	**0.331* (0.0001)**
Emotion Perception Index$^{\times}$	-0.049 (0.237)	0.033 (0.431)	0.012 (0.776)	0.002 (0.954)	-0.034 (0.439)
Facial Memory	0.082 (0.030)	0.041 (0.278)	-0.389* (0.0001)	0.133* (0.0001)	0.194* (0.0001)
Emotional Processing	-0.023 (0.551)	0.112 (0.003)	-0.410* (0.0001)	0.173* (0.0001)	0.286* (0.0001)

[2] Bolded indexes are factor scores based on age- and sex-corrected items. Site coding: 1 = PENN, 2 = PITT. Sex coding: 1 = Male, 2 = Female. Better performance is indicated by higher scores on functioning and cognition variables. $^{\times}$ correcting for General Cognition
***** Significance levels were adjusted for multiple comparisons using the Bonferroni correction ($p = 0.05/90 = 0.0006$).

3.3 DIAGNOSTIC GROUP DIFFERENCES

3.3.1 Mean Group Differences

At this stage of the analysis, pedigree members having Other psychiatric diagnoses were excluded as study questions focused on the Schizophrenia, Major Depression, Substance Abuse and No Diagnosis pedigree groups. As presented in Table 5, a one-way ANOVA examining diagnostic group differences in the Functioning index was significant and Tukey pairwise tests showed that the Schizophrenia group had the poorest Functioning compared to all other groups, which were rated similarly. Individual aspects of Functioning followed a generally similar pattern.

For the General Cognition index, the Schizophrenia group again performed most poorly and the Substance Abuse demonstrated performance that was significantly better than Schizophrenia but worse than the Control group. Individual aspects of General Cognition also followed a generally similar pattern.

For the Emotion Perception index, the Schizophrenia group performed significantly more poorly than all other groups. Furthermore, the No Diagnosis group demonstrated worse performance than the Controls. For both component items, the Schizophrenia group performed at a lower level than the other groups, which did not differ significantly from each other. After accounting for General Cognition, there were no significant differences among groups in Emotion Perception.

3.3.2 Group Differences in Variation

As shown in Table 5, pairwise Levene's tests of homogeneity of variances showed that the Schizophrenia group variance did not differ significantly relative to other groups for the Functioning index as well as the Marital Status and Living Situation items. Relative to all other groups, the Schizophrenia group had significantly less variation for Current Occupation and significantly more variation for Global Functioning.

Table 5. Mean group comparisons for functioning and cognition across groups. [3]

	SC	*MDD*	*SUD*	*ND*	*F*	*df*	*p*
Functioning Index	**-1.405 [a] (1.155)**	**0.268 [b] (1.082)**	**0.418 [b] (1.120)**	**0.162 [b] (1.100)**	**45.90**	**4, 580**	**0.0001**
Marital Status	-0.732 [a] (0.960)	0.345 [bc] (1.061)	0.424 [c] (1.100)	0.246 [bc] (1.007)	21.20	4, 579	0.0001
Living Situation	-1.251 [a] (1.268)	0.256 [b] (1.091)	0.395 [b] (1.148)	0.092 [b] (1.112)	30.61	4, 558	0.0001
Current Occupation	-1.931 [a] (0.763)	-0.252 [bc] (1.015)*	-0.515 [b] (1.101)*	-0.249 [bc] (0.996)*	94.19[+]	4, 200	0.0001
Global Functioning	-3.150 [a] (1.502)	-0.137 [b] (1.042)*	0.201 [bc] (1.048)*	0.572 [c] (0.814)*	128.53[+]	4, 178	0.0001
General Cognition Index	**-2.527 [a] (2.342)**	**-0.171 [bc] (0.949)***	**-0.569 [b] (1.147)***	**-0.425 [bc] (1.242)***	**22.98[+]**	**4, 195**	**0.0001**
Abstraction and Mental Flexibility	-1.357 [a] (1.212)	-0.077 [b] (0.884)	-0.299 [b] (0.984)	-0.208 [b] (0.896)	27.03	4, 562	0.0001
Attention	-1.953 [a] (2.037)	-0.188[bc] (1.114)*	-0.640 [b] (1.567)*	-0.247[bc] (1.165)*	14.97[+]	4, 174	0.0001
Verbal Memory	-1.385 [a] (1.883)	-0.252[bc] (0.938)*	-0.599 [b] (1.344)	-0.335 [bc] (1.211)*	10.02[+]	4, 184	0.0001
Spatial Memory	-1.120 [a] (1.561)	-0.081 [b] (1.114)	-0.393 [b] (1.142)	-0.290 [b] (1.178)	8.34[+]	4, 178	0.0001
Spatial Processing	-1.529 [a] (2.141)	-0.089 [b] (1.157)*	-0.394 [b] (1.143)*	-0.239 [b] (1.115)*	8.31[+]	4, 173	0.0001
Sensorimotor Dexterity	-1.816 [a] (2.144)	-0.180 [b] (0.906)*	-0.455 [b] (0.805)*	-0.311 [b] (1.102)*	12.98[+]	4, 188	0.0001
Trails A	-1.566 [a] (2.195)	0.004 [b] (0.901)*	-0.242 [b] (0.919)*	-0.273 [b] (1.316)*	9.82[+]	4, 197	0.0001
Trails B	-1.469 [a] (1.747)	-0.092 [b] (0.833)*	-0.086 [b] (1.004)*	-0.122 [b] (1.036)*	11.21[+]	4, 187	0.0001
California Verbal Learning Test	-1.066 [a] (1.394)	-0.037 [b] (1.240)	-0.356 [b] (1.294)	-0.047 [b] (1.078)	12.12	4, 514	0.0001
Emotion Perception Index	**-1.705 [a] (1.751)**	**-0.203[bc] (0.997)***	**-0.442[bc] (1.202)**	**-0.528 [b] (1.309)***	**17.50[+]**	**4, 190**	**0.0001**
Facial Memory	-1.239 [a] (1.807)	-0.066 [b] (1.060)*	-0.307 [b] (1.180)	-0.388 [b] (1.178)*	9.39[+]	4, 186	0.0001
Emotional Processing	-1.488 [a] (1.296)	-0.257 [b] (0.929)	-0.411 [b] (1.076)	-0.449 [b] (1.160)	21.35	4, 560	0.0001

[3] Note: All items and indexes were standardized to the total control group. Results of one-way ANOVAs are reported with the F-statistic or the Welch statistic, where appropriate, and the within-groups degrees of freedom (*df*). Given that all omnibus tests were significant at $p = 0.0001$, post-hoc Tukey's pairwise tests were conducted. Statistics sharing the same superscripts did not differ significantly ($p \leq 0.05$) from each other (i.e. were included in a homogeneous subset).

[+] indicates significant difference across groups in homogeneity of variance; Welch's statistic reported instead of F-statistic * denotes a significant difference in group variance relative to the variance of the Schizophrenia group at $p = 0.05$.

As shown in Figure 1, Functioning scores across groups appeared to be bimodal. Although approximately 84% of Functioning scores in Schizophrenia were negative (i.e. below the mean of Controls) and negative scores constituted less than half of this proportion in other diagnostic groups, 16% of Functioning scores in Schizophrenia were above the mean of Controls.

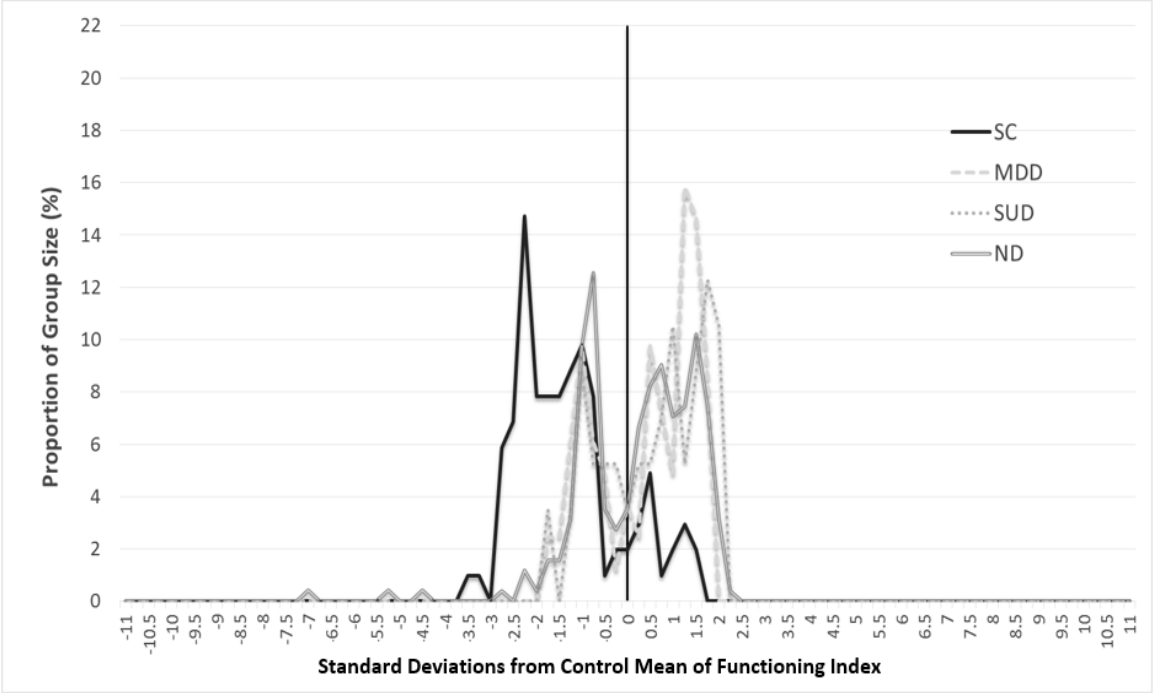

Figure 1. Distributions of scores on the Functioning index by pedigree group.

The Schizophrenia group showed approximately twice the variance in the General Cognition index relative to all other groups. This pattern generally held across all component tests except Abstraction and Mental Flexibility and the CVLT, for which there were no overall significant differences in variance. As shown in Figure 2, General Cognition scores across groups appeared to be unimodal with a negative skew. Approximately 86% of General Cognition scores in Schizophrenia were negative (with 14% above the control mean), while the proportion of negative scores approximated 60% in other diagnostic groups.

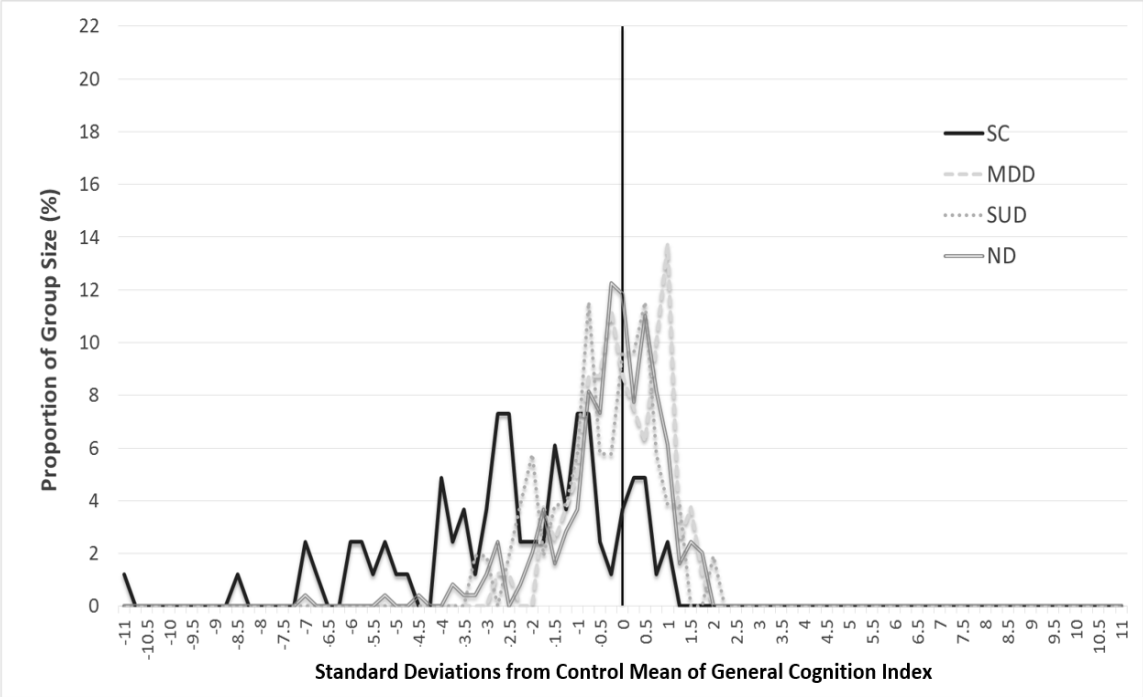

Figure 2. Distributions of scores on the General Cognition index by pedigree group.

The Schizophrenia group also showed approximately 50% more variation in the Emotion Perception index than all other groups except for the Substance Abuse group. This pattern also held for Facial Memory, although for Emotional Processing, there were no significant differences in variance compared to the Schizophrenia group. As shown in Figure 3, Emotion Perception scores across groups appeared to be unimodal with a negative skew. As with General Cognition, approximately 86% of Emotion Perception scores in Schizophrenia were negative (with 14% above control mean), while the proportion of negative scores approximated 60% in other diagnostic groups. All Emotion Perception standardized scores were less than 1.00 in Schizophrenia.

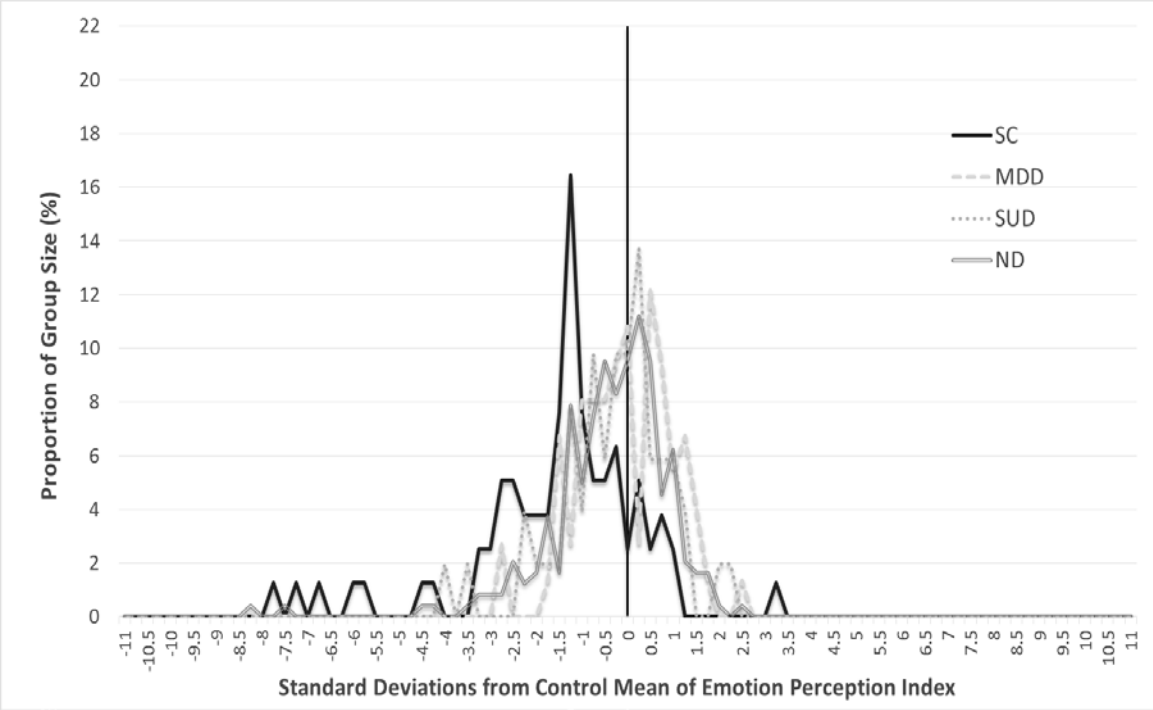

Figure 3. Distributions of scores on the Emotion Perception index by pedigree group.

Figure 4 shows that after accounting for General Cognition, the bin with the greatest proportion of Emotion Perception standardized scores in Schizophrenia ranged from 0.75 to 1.00, and all four diagnostic groups showed an approximately normal distribution centered around 0.

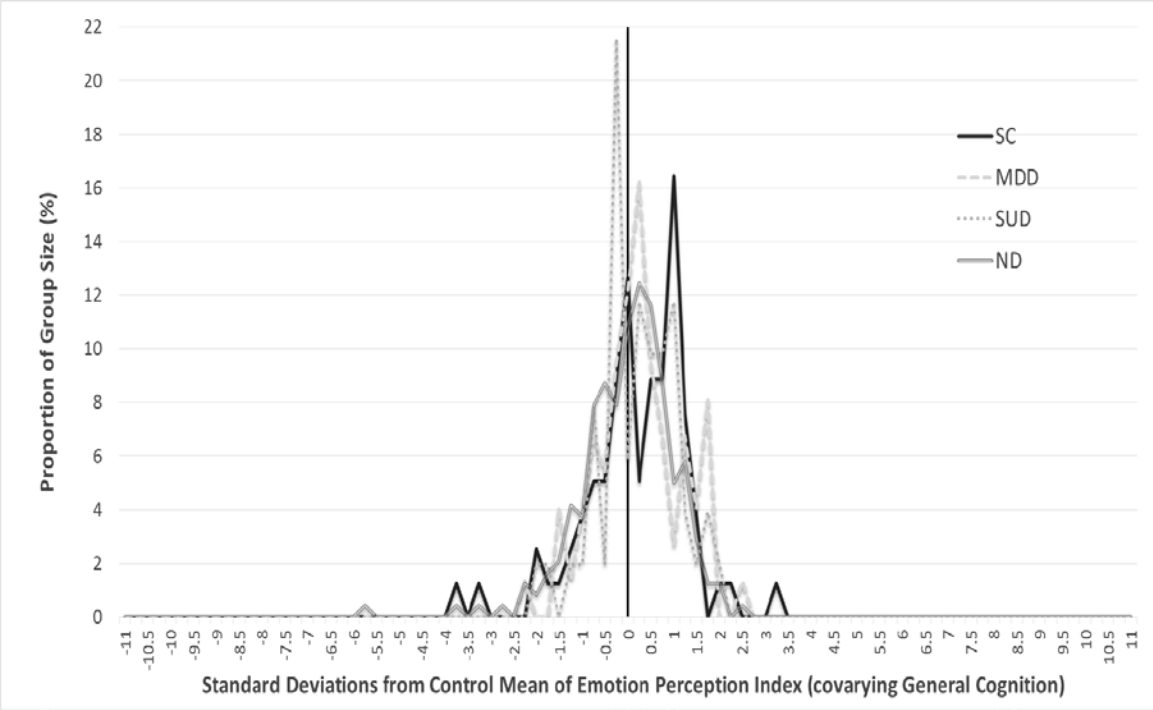

Figure 4. Distributions of scores on the Emotion Perception index, after accounting for General Cognition, by pedigree group.

3.4 HERITABILITY WITHIN DIAGNOSIS

Variance component based quantitative trait analyses were performed using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) program version 4.0.7 (Almasy & Blangero, 1998). Heritability coefficients for the three indexes and their component items calculated using SOLAR are presented in Table 6. Covariates of age and sex were included in all analyses, and the additional covariate of education did not change the overall pattern of results.

The Functioning Index yielded low heritability estimates across all diagnostic groups except for Schizophrenia, for which it was significantly heritable. Current Occupation and Global Functioning were significantly heritable in the Schizophrenia and No Diagnosis groups.

General Cognition was significantly heritable in Schizophrenia but not in any other group although there was a nonsignificant trend for Major Depression. All Cognition tests were significantly heritable among Schizophrenia participants. Attention, Spatial Processing, Sensorimotor Dexterity and Trails A were significantly heritable in Major Depression but no Cognition tests were significantly heritable in Substance Abuse. In the No Diagnosis group, all tasks except for Abstraction and Mental Flexibility, Spatial Processing and Trails B were significantly heritable.

Emotion Perception and its component items were all highly heritable in the Schizophrenia and No Diagnosis groups but not in the Major Depression and Substance Abuse groups. The heritability estimates for Schizophrenia were approximately twice as large as those for No Diagnosis. After covarying General Cognition, Emotion Perception was heritable only in No Diagnosis, although there was a trend in Schizophrenia. Results of the reverse analyses, examining General Cognition after covarying Emotion Perception, are presented in Appendix Table 9.

Table 6. Heritabilities for functioning and cognition in different diagnostic groups.[4]

	SC	*MDD*	*SUD*	*ND*
Functioning Index	0.481* (0.029)	0.000 (0.500)	0.000 (0.500)	0.004 (0.484)
Marital Status	0.306 (0.143)	0.573* (0.041)	0.000 (0.500)	0.079 (0.231)
Living Situation	0.386 (0.066)	0.000 (0.500)	0.000 (0.500)	0.000 (0.500)
Current Occupation	0.970* (0.0001)	0.334 (0.249)	0.970* (0.027)	0.394* (0.002)
Global Functioning	1.000* (0.0001)	0.147 (0.346)	0.000 (0.500)	0.489* (0.0001)
General Cognition Index	1.000* (0.0001)	0.586 (0.057)	0.381 (0.169)	0.146 (0.092)
Abstraction and Mental Flexibility	1.000* (0.0001)	0.000 (0.500)	0.360 (0.295)	0.122 (0.184)
Attention	0.694* (0.007)	0.670* (0.023)	0.390 (0.200)	0.316* (0.011)
Verbal Memory	0.671* (0.008)	0.000 (0.500)	0.306 (0.226)	0.393* (0.005)
Spatial Memory	0.608* (0.019)	0.000 (0.500)	0.000 (0.500)	0.358* (0.004)
Spatial Processing	0.740* (0.008)	0.715* (0.033)	0.307 (0.251)	0.090 (0.260)
Sensorimotor Dexterity	1.000* (0.0001)	0.909* (0.038)	0.256 (0.330)	0.345* (0.006)
Trails A	0.825* (0.001)	1.000* (0.028)	0.000 (0.500)	0.333* (0.002)
Trails B	0.980* (0.0001)	0.000 (0.500)	0.655 (0.193)	0.035 (0.390)
California Verbal Learning Test	0.432* (0.037)	0.000 (0.500)	0.000 (0.500)	0.538* (0.001)
Emotion Perception Index	0.941* (0.0001)	0.386 (0.224)	0.077 (0.424)	0.518* (0.0001)
Emotion Perception Index[×]	0.569 (0.058)	0.000 (0.500)	0.522 (0.192)	0.461* (0.003)
Facial Memory	0.795* (0.003)	0.637 (0.102)	0.000 (0.500)	0.318* (0.012)
Emotional Processing	0.744* (0.006)	0.356 (0.231)	0.350 (0.215)	0.460* (0.001)

[4] Univariate heritability analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed) [×] additional covariate: General Cognition

3.5 CORRELATIONS WITHIN DIAGNOSIS

3.5.1 Phenotypic Correlations within Diagnosis

Phenotypic correlations among the three indexes calculated using SOLAR are presented in Table 7. Analyses including the additional covariate of education did not change the overall pattern of results. Phenotypic correlations between General Cognition and Functioning were significantly greater than zero for the Schizophrenia, Major Depression, and No Diagnosis groups. Except for the correlation in Substance Abuse being significantly less than that in No Diagnosis, these correlations did not differ significantly from each other when comparing among all diagnostic groups using one-sided tests of Fisher's r-to-Z transformations (see Appendix Table 5).

Similarly, phenotypic correlations between Emotion Perception and Functioning were significantly greater than zero for the Schizophrenia and No Diagnosis groups and did not differ significantly from each other when comparing among diagnostic groups. After controlling for General Cognition, the phenotypic correlations between Emotion Perception and Functioning decreased in magnitude and were no longer significant for any group.

Phenotypic correlations between Functioning and Cognition items for each pedigree group are shown in the Appendix Table 6. In Schizophrenia, the Functioning index and its component items, Living Situation and Global Functioning, demonstrated moderate positive correlations with five of nine Cognition tests, while Marital Status and Current Occupation were generally uncorrelated with Cognition tests. In contrast, in Major Depression, the Functioning index and all Functioning items except for Current Occupation were correlated only with one Cognition test. In Substance Abuse, the Functioning index was correlated with only one Cognition test whereas Global Functioning showed positive correlations with most Cognition tests. In No Diagnosis, most Functioning items were correlated with many Cognition tests.

3.5.2 Genetic Correlations within Diagnosis

Genetic correlations among the three indexes calculated using SOLAR are presented in Table 7. As with the phenotypic correlations, analyses including the additional covariate of education did not change the overall pattern of results. The genetic correlations between General

Cognition and Functioning were positive and significant in Schizophrenia but nonsignificant in other groups. Similarly, the genetic correlation between Emotion Perception and Functioning was positive and significant in Schizophrenia but not other groups.

Genetic correlations between Functioning and Cognition items and indexes for each pedigree group are shown in the Appendix Table 7. In Schizophrenia, the Functioning index and all Functioning items except for Marital Status were genetically correlated with all General Cognition and most Emotion Perception tests. In contrast, in Major Depression, the Functioning index and all Functioning items did not show significant genetic correlations with any Cognition indexes or tests. In Substance Abuse, Current Occupation demonstrated genetic correlations with almost all General Cognition and Emotion Perception indexes and tests whereas other Functioning items were not significantly correlated with Cognition tests. Like Major Depression, there were few significant genetic correlations among Functioning and Cognition items in No Diagnosis.

3.5.3 Environmental Correlations within Diagnosis

Environmental correlations among the three indexes calculated using SOLAR are presented in Table 7. As with the phenotypic correlations, analyses including the additional covariate of education did not change the overall pattern of results. The environmental correlation between General Cognition and Functioning was significant (and positive) only in the No Diagnosis group. Similarly, the environmental correlation between Emotion Perception and Functioning was significant (and positive) only in the No Diagnosis group. After controlling for General Cognition, there was a nonsignificant trend only for a positive environmental correlation between Emotion Perception and Functioning in Schizophrenia.

Environmental correlations between Functioning and Cognition items and indexes for each pedigree group are shown in the Appendix Table 8. In Schizophrenia, the Functioning index or items were correlated with only one Cognition test (and negatively). In Major Depression, Marital Status was environmentally correlated with only three Cognition tests. In Substance Abuse, only Global Functioning demonstrated significant environmental correlations with a few Cognition tests. In No Diagnosis, Living Situation showed modest positive

environmental correlations with General Cognition and Emotion Perception and half of their component tests.

Table 7. Phenotypic, genetic and environmental correlations among the general cognition, emotion perception and functioning indexes within diagnostic groups in the pedigree sample.[5]

		SC	*MDD*	*SUD*	*ND*	*Controls*
R_P	General Cognition/ Functioning	0.335* (0.005)	0.245* (0.037)	0.084 (0.542)	0.333* (0.0001)	0.066 (0.571)
	Emotion Perception/ Functioning	0.301* (0.013)	0.183 (0.114)	0.261 (0.076)	0.185* (0.006)	0.033 (0.747)
	Emotion Perception/ Functioning[×]	0.031 (0.795)	0.053 (0.649)	0.257 (0.064)	-0.014 (0.837)	0.004 (0.971)
R_G	General Cognition/ Functioning	0.956* (0.0001)	1.000 (0.896)	1.000 (0.610)	1.000 (0.852)	
	Emotion Perception/ Functioning	0.564* (0.016)	-1.000 (0.756)	0.094 (1.000)	-1.000 (0.677)	
	Emotion Perception/ Functioning[×]	-0.783 (0.104)	-1.000 (0.746)	-1.000 (0.413)	-1.000 (0.659)	
R_E	General Cognition/ Functioning	-1.000 (0.072)	0.179 (0.610)	-0.042 (0.847)	0.269* (0.005)	
	Emotion Perception/ Functioning	-0.364 (0.649)	0.241 (0.178)	0.102 (0.498)	0.244* (0.008)	
	Emotion Perception/ Functioning[×]	0.719 (0.051)	0.107 (0.645)	0.359 (0.179)	0.062 (0.676)	

[5] R_P: Phenotypic correlation; R_G: Genetic correlation; R_E: Environmental correlation.
Phenotypic correlations were conducted without Controls while genetic and environmental correlations were conducted with Controls in SOLAR.
Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)
[×] additional covariate: General Cognition

3.6 CORRELATIONS ACROSS DIAGNOSES

3.6.1 Predicting Schizophrenia Functioning from Cognition in Other Diagnoses

Genetic correlations between Schizophrenia Functioning and General Cognition or Emotion Perception in the Major Depression, Substance Abuse and No Diagnosis groups conducted in SOLAR are presented in Table 8. (The approximate number of within-family pairings made between Schizophrenia and relatives of other diagnostic groups are shown in Appendix Table 6.) None of the genetic correlations between the indexes differed significantly from zero, indicating that Functioning in Schizophrenia is not genetically associated with Cognition in other diagnoses.

Environmental correlations between Schizophrenia Functioning and General Cognition or Emotion Perception in the Major Depression, Substance Abuse and No Diagnosis groups conducted are also presented in Table 8. Again, none of the environmental correlations between the indexes differed significantly from zero, indicating that Functioning in schizophrenia is not environmentally associated with Cognition in other diagnoses.

Table 8. Genetic and environmental correlations between schizophrenia functioning and cognition in other diagnostic groups within the pedigree sample. [6]

	Cognition					
SC Functioning	*MDD*		*SUD*		*ND*	
	General Cognition	Emotion Perception	General Cognition	Emotion Perception	General Cognition	Emotion Perception
R_G	0.235 (0.684)	-0.307 (0.682)	1.000 (0.114)	1.000 (0.238)	-0.254 (0.642)	0.453 (0.203)
R_E	-0.114 (0.865)	0.253 (0.703)	-0.375 (0.401)	-0.481 (0.333)	0.478 (0.224)	-0.282 (0.575)

[6] R_G: Genetic correlation; R_E: Environmental correlation.
Analyses conducted in SOLAR with Controls. Covariates include age and sex, with p-values indicated in parentheses.

3.6.2 Predicting Schizophrenia Cognition from Functioning in Other Diagnoses

Genetic correlations between Schizophrenia Functioning and Cognition in the Major Depression, Substance Abuse and No Diagnosis groups are presented in Table 9. No genetic correlations were significant, indicating that Cognition in schizophrenia is not genetically associated with Functioning in other diagnoses.

Environmental correlations between Schizophrenia Functioning and Cognition in the Major Depression, Substance Abuse and No Diagnosis groups are also presented in Table 9. None of the environmental correlations between the indexes differed significantly from zero, indicating that Cognition in Schizophrenia is not environmentally associated with Functioning in other diagnoses.

Table 9. Genetic and environmental correlations between schizophrenia cognition and functioning across diagnostic groups within the pedigree sample.[7]

		Functioning		
SC		*MDD*	*SUD*	*ND*
R_G	General Cognition	-1.000 (0.227)	-1.000 (0.895)	-1.000 (0.965)
	Emotion Perception	-1.000 (0.091)	-0.332 (1.000)	-1.000 (0.418)
R_E	General Cognition	1.000 (0.251)	0.183 (0.878)	0.047 (0.943)
	Emotion Perception	1.000 (0.130)	0.061 (0.873)	0.332 (0.510)

[7] R_G: Genetic correlation; R_E: Environmental correlation.
Analyses conducted in SOLAR with Controls. Covariates include age and sex, with p-values indicated in parentheses.

3.7 EXPLORATORY MEDIATION ANALYSES

Given the significant genetic correlations between Functioning and Cognition in Schizophrenia, Negative Symptoms and Positive Symptoms were examined separately as potential mediators (see Figure 5). The SANS summary score or SAPS summary score was entered as an additional covariate in the following analyses conducted in SOLAR. Ninety-one Schizophrenia participants (88.3%) and 42 Controls (31.1%) (all of whom were recruited from PITT) had SANS and SAPS summary scores; none were missing more than half of the SANS global scores and more than half of the SAPS global scores.

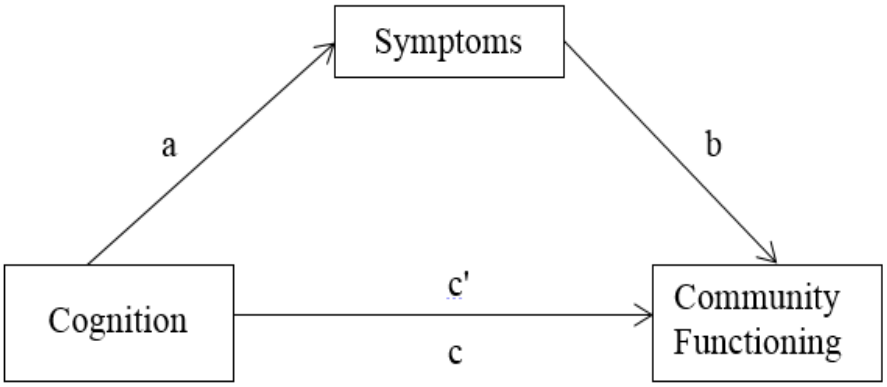

Figure 5. Schematic of the hypothesized pathway between Cognition and Functioning, with Symptoms as the mediator.

Results of the exploratory mediational analyses with Negative Symptoms and Positive Symptoms are shown in Table 10. The phenotypic and genetic correlations between Functioning and Cognition in Schizophrenia were positive and similar in magnitude to the overall Schizophrenia sample (see Table 7), providing support for the representativeness of this subsample. While the environmental correlation between General Cognition and Functioning in the overall sample matched that found in this subsample, the environmental correlation between Emotion Perception and Functioning was opposite in sign.

As SOLAR does not provide standard errors for the point estimates of the phenotypic correlations, partial mediation was inferred according to the following criteria (Baron & Kenny, 1986): 1) a significant correlation existed between Symptoms and Functioning after accounting for Cognition; 2) a significant correlation between Functioning and Cognition became nonsignificant after covarying symptoms; and 3) a significant correlation between Cognition and Symptoms remained significant after covarying Functioning (to rule out "reverse" mediation). None of the twelve sets of correlations met all three criteria, suggesting that the relationship between Functioning and Cognition is not partially mediated by negative or positive symptoms.

Table 10. Correlations between cognition and functioning, with negative symptoms and positive symptoms as separate mediators. [8]

		General Cognition			*Emotion Perception*		
	Correlation	**R_P**	**R_G**	**R_E**	**R_P**	**R_G**	**R_E**
Negative Symptoms	Cognition/ Functioning	0.317* (0.010)	1.000* (0.0001)	-1.000 (0.263)	0.292* (0.020)	0.423 (0.542)	0.384 (0.481)
	Cognition/ Functioning[×]	0.236 (0.052)	1.000 (0.250)	-0.063 (0.845)	0.221 (0.080)	-1.000 (0.280)	0.562* (0.006)
	Cognition/ Symptoms	-0.348* (0.007)	-0.715* (0.0001)	1.000 (0.414)	-0.239 (0.155)	-0.758* (0.0001)	1.000 (0.512)
	Cognition/ Symptoms[◊]	-0.280* (0.033)	-0.625 (0.180)	1.000 (0.425)	-0.157 (0.224)	-0.656* (0.0001)	1.000 (0.425)
	Symptoms/ Functioning	-0.362* (0.0001)	-0.856* (0.0001)	1.000 (0.876)	-0.362* (0.0001)	-0.856* (0.0001)	1.000 (0.876)
	Symptoms/ Functioning[+]	-0.260 (0.103)	-0.885* (0.0001)	1.000 (0.399)	-0.274 (0.057)	-0.847* (0.0001)	1.000 (0.109)
Positive Symptoms	Cognition/ Functioning	0.317* (0.010)	1.000* (0.0001)	-1.000 (0.263)	0.292* (0.020)	0.423 (0.542)	0.384 (0.481)
	Cognition/ Functioning[×]	0.262* (0.035)	1.000 (0.236)	-0.059 (0.861)	0.226 (0.072)	-1.000 (0.301)	0.462* (0.012)
	Cognition/ Symptoms	-0.265* (0.035)	-0.903* (0.0001)	1.000 (0.058)	-0.286* (0.024)	-1.000* (0.0001)	1.000 (0.108)
	Cognition/ Symptoms[◊]	-0.178 (0.159)	-0.893* (0.0001)	1.000 (0.205)	-0.211 (0.106)	-1.000* (0.0001)	1.000 (0.118)
	Symptoms/ Functioning	-0.303* (0.005)	-0.845* (0.0001)	1.000 (0.726)	-0.303* (0.005)	-0.845* (0.0001)	1.000 (0.726)
	Symptoms/ Functioning[+]	-0.304* (0.012)	0.040 (0.972)	-0.484 (0.166)	-0.305* (0.015)	-0.364 (0.345)	-0.198 (0.682)

[8] Phenotypic correlations were conducted in a Schizophrenia-only sample ($N = 91$), while genetic and environmental correlations were conducted with Schizophrenia and Controls ($N = 133$) that had SANS or SAPS summary scores in SOLAR. Covariates include age and sex, with p-values indicated in parentheses.
[+]additional covariate: Cognition [×]additional covariate: Symptoms [◊]additional covariate: Functioning *$p < 0.05$ (two-tailed)

4.0 DISCUSSION

4.1 SUMMARY OF FINDINGS

The results of the current study suggest that the cognition-functioning correlation arises largely from genetic factors rather than nonshared environmental influences in schizophrenia whereas this was not the case in major depression, substance abuse, or no psychopathology. In this community-based, multigenerational sample of families with at least two relatives affected with schizophrenia, the following points were noted:

1) As predicted, schizophrenia showed significantly poorer average functioning and cognition than all other groups, even major depression and substance abuse.
2) Individual differences in functioning and cognition were significantly heritable in schizophrenia but largely nonsignificant in other diagnostic groups, indicating that variation in both functioning and cognition are importantly attributable to genetic factors in schizophrenia.
3) Cognition-functioning phenotypic correlations were significant and approximated 0.3 in schizophrenia, major depression and no diagnosis groups, but did not differ significantly from zero for substance abuse or controls.
4) Cognition-functioning genetic correlations were large and significant only for schizophrenia but not other diagnostic groups, suggesting that the cognition-functioning phenotypic correlation arises largely from genetic factors in schizophrenia.
5) In contrast, cognition-functioning environmental correlations were significant only in the no diagnosis group, but not in other groups, suggesting that the cognition-functioning phenotypic correlation is not attributable to individual-specific environmental factors in schizophrenia.

6) Genetic and environmental correlations between schizophrenia functioning and cognition in other relative groups were nonsignificant, indicating that the cognition-functioning genetic correlation is largely specific to schizophrenia.
7) Exploratory analyses suggested that none of the phenotypic, genetic or environmental cognition-functioning correlations were mediated by negative or positive symptoms in schizophrenia.
8) Overall, social cognition as measured in this study performed similarly to general cognition and certainly not better. Furthermore, after accounting for general cognition, social cognition did not differ significantly in means nor variances among groups, was not significantly heritable in any group except no diagnosis, and did not produce significant phenotypic, genetic or environmental correlations with functioning in any group, within or across diagnoses, suggesting that the contribution of general cognition to functioning largely comprises the contribution of social cognition.

4.2 THE NATURE OF FUNCTIONING AND COGNITION ACROSS DIAGNOSTIC GROUPS

While they were sufficiently asymptomatic to live in the community at the time of the study, individuals with schizophrenia still demonstrated significant mean deficits in functioning even compared to their relatives with serious non-psychotic psychopathologies of major depression or substance abuse, who themselves functioned more poorly in functioning than their relatives without a diagnosis. This is consistent with previous research in community-based samples finding greater functional impairments in schizophrenia than in major depression or bipolar disorder (Bartels, Mueser, & Miles, 1997; Bowie et al., 2010).

Despite this average functioning deficit, individual differences were substantial, with approximately one in six individuals with schizophrenia even demonstrating better functioning than the control mean. This parallels findings from other studies showing that almost half of individuals with schizophrenia are gainfully employed at least half of the time in the year before hospitalization (Racenstein et al., 2002; Strauss & Carpenter, 1974) and in the decade following hospitalization (Racenstein et al., 2002), irrespective of their concurrent symptom status.

As expected (Gold & Dickinson, 2013; Heinrichs & Zakzanis, 1998), schizophrenia patients exhibited even more striking deficits in cognitive test performance, approximating 1.5 to 2 standard deviations, compared to other diagnostic groups and controls. This accords with previous studies which find greater cognitive deficits in schizophrenia than in other diagnoses, including affective psychosis (Reichenberg et al., 2009; Schretlen et al., 2007)

Individuals with schizophrenia not only showed poorer cognitive performance on average than others, as with functioning, they also showed substantial variation, and even more than other groups. Although most performed below the control mean, approximately one out of six individuals with schizophrenia demonstrated even better cognitive performance than the control means, consistent with studies finding that a minority of individuals with schizophrenia perform at or above the control averages (Holthausen et al., 2002; Seaton, Allen, Goldstein, Kelley, & van Kammen, 1999). This is also consistent with previous studies demonstrating that a notable proportion of individuals with schizophrenia demonstrate "neuropsychological normality", or scores on standardized cognitive tests within range of normal cognitive performance (Joyce & Roiser, 2007).

Given that emotion perception showed similar features to general cognition in this study, discussion of findings concerning social cognition specifically will be consolidated in section 4.6.

4.3 ETIOLOGICAL INFLUENCES ON FUNCTIONING AND COGNITION

In this study, our overall index of functioning and the global functioning measure were heritable among individuals with schizophrenia (h^2=0.48, and h^2=1.00, respectively). This aligns with the only study to date combining multiple current functioning measures into a composite score, which showed a heritability approximating 0.61 in a disability/ impairment factor consisting of illness severity along with occupational and relationship functioning among concordant relatives (McGrath et al., 2009). Our findings are also consistent with six studies that have examined global functioning in concordant relatives, of which all but one demonstrated that current or worst global functioning, as measured by the Global Assessment of Functioning (Cardno et al., 1998; Vassos et al., 2008) or similar measures of recovery and deterioration (Burke et al., 1996;

Kendler et al., 1997; Wickham et al., 2002) are familial in schizophrenia, the sole exception being a cross-cultural study (Deshpande et al., 2004).

In terms of domains of functioning, the current study found occupational status was highly heritable in schizophrenia, while marital status and independent living were not. In contrast, both of the two extant studies examining the familiality of occupational status in concordant relatives found null results (Bhatia et al., 2004; Deshpande et al., 2004); although the Indian samples from both studies may reflect different environmental effects than those in North American samples such as ours. Our null findings for marital status parallel those of the two previous studies, none of which have found marital status to be familial (Cardno et al., 1998; Deshpande et al., 2004), although marital status in schizophrenia was found to be familial in an Indian sample (Deshpande et al., 2004). Finally, contrary to our null findings, independent living in schizophrenia was moderately familial in the only extant study, conducted in an Indian sample (Deshpande et al., 2004).

Overall, our findings are generally consistent with emerging literature suggesting that 1) functioning, as measured by composite variables and global functioning ratings, is at least moderately heritable in schizophrenia after illness onset, and 2) certain domains of functioning such as occupational status may be more influenced by genetic effects than others. While genetic effects on functioning have not been widely studied in schizophrenia, such effects on functioning have not been studied at all in major depression or substance abuse. In the general population, genetic effects on functioning measures such as income and occupational status yield heritabilities approximating 0.4 (Rowe, Vesterdal, & Rodgers, 1998; Weinert & Hany, 2000), on par with the heritability of 0.4 for current occupation found in our study for schizophrenia.

General cognition in schizophrenia was highly heritable in this study, with heritabilities greater than 0.6 for all but one of the cognitive domains. This accords with findings from the only study to date examining correlations among relatives affected with schizophrenia (Hoff et al., 2005), which included only 17 concordant sib-pairs and did not include a measure of general cognitive ability. This study found moderate within-pair correlations for executive functioning ($r \approx 0.6$) and only for certain measures, while all visual memory tests, all verbal memory tests, and the majority of perceptual-motor speed tests were not significantly correlated within concordant pairs (Hoff et al., 2005). Altogether, given the greater power in our larger, multiplex, multigenerational family design to detect the contribution of genetic effects to cognition, our

findings extend those of the previous study (Hoff et al., 2005), demonstrating that both specific and overall measures of general cognition are at least moderately attributable to genetic effects in schizophrenia.

Contrary to our findings for schizophrenia, general cognition was not significantly heritable in other diagnostic groups, although there was a trend towards significance in major depression. However, four out of nine of the general cognitive tests were heritable in major depression and the majority of these tests were heritable in relatives without psychopathology. Although no study to date has examined the heritability of cognition in major depression or substance abuse, our results for relatives without psychopathology are generally consistent with meta-analyses of studies in the general population have found the heritability of IQ to approximate 50% (Chipuer, Rovine, & Plomin, 1990; Devlin, Daniels, & Roeder, 1997; Haworth et al., 2009). Overall, there are strong genetic effects on cognition within individuals with schizophrenia and their relatives with major depression and more moderate genetic effects in relatives without psychopathology.

4.4 ETIOLOGICAL INFLUENCES ACROSS FUNCTIONING AND COGNITION

In the current study, the cognition-functioning phenotypic correlation in schizophrenia approximated the estimates provided in the most recent meta-analysis (Fett et al., 2011). With regards to relatives having other diagnoses, we found significant cognition-functioning phenotypic correlations in major depression but not for substance abuse. As with schizophrenia, cognition has been implicated as the most important contributor to psychosocial functioning (with employment in particular) in major depression (McIntyre et al., 2013). In contrast, while a multitude of studies have examined cognition as a predictor of clinical outcome (i.e. abstinence and relapse) in substance abuses, none have directly examined the cognition-functioning correlation. Relatives without psychopathology also showed a significant cognition-functioning phenotypic correlation in this study, which is consistent with studies describing general cognitive ability as the best predictor of occupational status in the general population (Schmidt & Hunter, 2004) and pinpointing phenotypic correlations between general cognitive ability and occupational status or income approximating 0.3 (Rowe et al., 1998; Tambs, Sundet, Magnus, &

Berg, 1989; Weinert & Hany, 2000), although the cognition-functioning correlation was not significant in controls. Overall, our study stands with the literature emphasizing cognition as a crucial predictor of functioning across schizophrenia, major depression and the general population.

The large and highly significant cognition-functioning genetic correlation in schizophrenia suggests that genetic factors impacting functioning overlap almost entirely with genetic factors affecting cognition in schizophrenia. In contrast, this genetic correlation was not significant in relatives with major depression, substance abuse or no psychopathology, and furthermore, the environmental correlation was significant in relatives without psychopathology. Beyond the significant cognition-functioning genetic correlation within schizophrenia, functioning in schizophrenia was not significantly predicted by variation in cognition in relatives with other disorders. Thus, genetic effects on functioning in schizophrenia primarily overlap with genetic effects on cognition in schizophrenia but not with cognition in other psychopathology.

Overall, the significant cognition-functioning genetic correlation within schizophrenia and the nonsignificant correlations between functioning in schizophrenia and cognition in relatives with other diagnoses converge to suggest that the genetic basis of the cognition-functioning correlation is relatively specific to schizophrenia and is not shared with relatives with other psychopathology or lack of psychopathology.

4.5 THE CONTRIBUTION OF SYMPTOMS TO THE COGNITION-FUNCTIONING CORRELATION

In this study, we did not find evidence of symptoms acting as important mediators between cognition and functioning in schizophrenia. This contradicts findings from a recent meta-analysis suggesting that negative symptoms may mediate the cognition-functioning phenotypic correlation (Ventura et al., 2009). Symptoms ratings were only available for individuals recruited from PITT, restricting the sample size for these analyses. Ours is consistent with the hypothesis that negative symptoms and cognition may have separate but correlated etiologies (Harvey, Koren, Reichenberg, & Bowie, 2006) and may thus influence functioning through

distinct pathways. The hypothesis of symptoms mediating the cognition-functioning correlation deserves a more thorough investigation in longitudinal studies of schizophrenia relatives across different phases of the disorder.

4.6 SEPARATING THE CONTRIBUTION OF SOCIAL COGNITION FROM GENERAL COGNITION TO FUNCTIONING

The results of this study argue against social cognition as a unique predictor of functioning beyond general cognition in schizophrenia in contrast to several other studies (Schmidt et al., 2011). After accounting for general cognition, the lack of differences in means and variances across groups in social cognition translated into reduced and insignificant genetic correlations between social cognition and functioning in schizophrenia. The converse did not hold; after accounting for social cognition, general cognition retained a significant genetic correlation with functioning in schizophrenia (see Appendix Table 9). Our null results may reflect that our measures tap only a limited aspect of social cognition, emotion perception, and that other aspects, such as theory of mind, are more important for functioning.

4.7 STRENGTHS AND LIMITATIONS

To our knowledge, this is the first study to examine the etiological basis of the cognition-functioning correlation in schizophrenia. The large, multigenerational, multiplex family sample is a powerful study design that bears several advantages over previously reported studies. Given that participants were recruited from the community across multiple geographic regions, this study may reflect a wider range of functioning and cognition than may be found in studies that are limited to hospitals or supervised treatment centers. Furthermore, this study compared schizophrenia to two forms of psychopathology as well as lack of psychopathology. The measures also encompass a breadth of domains for both cognition and functioning; the cognition tests span both computerized and pencil-and-paper tasks, while the functioning measures of

marital status, living situation and current occupation are objective and are less liable to observer bias or demand characteristics than clinician- or self-report measures of functioning.

Despite these strengths, there are some limitations to the study. A limitation of the functioning index is that the global functioning rating was based on both overall functioning and symptoms; given that global functioning had the highest loading on the functioning index, some of the high heritability estimates and genetic correlations with the functioning index may reflect the contribution of symptoms. However, as we did not find symptoms to even partially mediate the cognition-functioning correlation, it appears that cognition does not act through symptoms to explain variation in functioning. At noted above, given that our study examined emotion perception, which is only one domain of social cognition and which may not be a unique predictor of functioning beyond general cognition. More comprehensive measures of social cognition might find stronger associations with functioning.

Furthermore, there are assumptions inherent in family study designs that may affect the inferences made from heritability estimates. Specifically, heritability estimates encompass resemblance for an observed trait between relatives that follow additive effects (e.g. similarity between relatives reduced on average by half with each degree of relation). To the extent that shared environmental effects act in this additive manner, they are confounded with heritability. In particular, shared environmental effects on cognition and functioning in adults may be impacted by factors such as socioeconomic status. However, the cognition-functioning genetic correlation did not span across relatives with different diagnoses, suggesting that general shared environmental effects contribute little to the cognition-functioning genetic correlation in schizophrenia. Nevertheless, without adoptive relatives, these effects cannot be resolved definitely.

In this study, the group sizes for major depression and especially substance abuse were smaller than that of schizophrenia, and thus, it is possible that the lack of significant genetic and cognition-functioning environmental correlations was due to insufficient power in these groups. Furthermore, the pedigree sample may not be representative of all individuals having major depression or substance abuse, nor individuals without a family history of schizophrenia. While the unique, multiplex nature of the families is a key part of this study and allows the examination of resemblance between affected relatives, it also presents a weakness as it may limit the generalizability of these findings beyond individuals with two relatives having schizophrenia. It

is also important to note that the sample was restricted to European-American individuals and may not generalize to other ethnicities.

Although medication status has been previously shown to have minimal effects on cognitive performance (Mojtabai et al., 2000), it is possible that medication may confound the cognition-functioning phenotypic correlation. Individuals who demonstrate poor functioning may be more symptomatic and may thus be prescribed higher doses of medications, which may in turn impact cognition, or conversely, individuals who have cognitive deficits may struggle to adhere to a medication regimen, which may lead to problems with functioning. Nevertheless, such medication effects would not confound estimates of genetic correlations, and instead would contribute to environmental correlations, which were not significant.

It is important to note that due to the cross-sectional nature of this study, we cannot resolve the sources of the cognition-functioning genetic correlation observed here in schizophrenia. This genetic correlation could arise by any of three possibilities (not mutually exclusive): 1) genetic effects on cognition, which have direct causal effects on functioning, 2) genetic effects on functioning, which have direct causal effects on cognition, and 3) shared genetic effects that affect both cognition and functioning. Longitudinal studies are important in distinguishing among the alternatives.

4.8 IMPLICATIONS

Standing alone as a basic study, our findings simply characterize traits and do not bear direct relevance to treatment implications except to suggest that, to be effective, environmental manipulations should be novel (e.g. Eack, Pogue-Geile, Greenwald, Hogarty, & Keshavan, 2011). The largely genetic basis of the cognition-functioning phenotypic correlation in schizophrenia suggests the importance of attempting to identify specific gene variants that may contribute to this association. Furthermore, the specificity of the cognition-functioning genetic correlation to schizophrenia suggests that such gene variants may contribute to risk for schizophrenia by overlapping with schizophrenia risk genes or by interacting with the schizophrenia risk genes to produce schizophrenia (as genetic modifiers). Thus, schizophrenia risk variants identified in genome wide association studies (GWAS) of schizophrenia

(Schizophrenia Working Group of the Psychiatric Genomics, 2014) may provide useful candidates rather than variants associated with cognition more generally. It must be remembered however, that the cognition-functioning correlation only encompasses a portion of the total variation in functioning in schizophrenia and that novel treatments should also be examined in conjunction with other factors that also impact functioning to maximize treatment gains.

APPENDIX

SUPPLEMENTARY TABLES

Appendix Table 1. Distribution of family size in the pedigree sample.

Family Size*	Number of Families
2	2
3	3
4	1
5	1
6	2
7	4
8	4
9	1
10	3
11	1
12	2
13	2
14	1
15	2
16	3
17	1
20	1
23	1
24	2
29	1
32	1
34	1
36	1
43	1
70	1
Mean	*15*
SD	*13*

*Family size includes members with diagnostic information who had at least one functioning or cognition variable

Appendix Table 2. Number of participants in the total sample with missing data.

		Number of Missing Cases for Functioning Variables					
		0	1	2	3	4	*Total*
Number of Missing Cognitive Variables	0	464	29	1	1	44	*539*
	1	114	11	0	1	5	*131*
	2	11	4	0	0	0	*15*
	3	7	2	0	0	1	*10*
	4	2	0	0	0	0	*2*
	5	1	1	0	0	0	*2*
	6	0	0	0	2	0	*2*
	7	1	1	0	0	0	*2*
	8	8	1	2	0	0	*11*
	9	5	1	0	0	0	*6*
	10	1	1	0	0	0	*2*
	11	42	7	2	0	0	*51*
	Total	*656*	*58*	*5*	*4*	*50*	*773*

Appendix Table 3. Diagnostic composition of pedigree sample by family.

Number in Diagnostic Group in Family	*Number of Families*			
	SC	*MDD*	*SUD*	*ND*
0	1	16	21	7
1	4	9	11	3
2	27	8	4	7
3	5	0	1	1
4	2	3	3	2
5	3	4	1	4
6	0	2	1	3
7	1	0	0	2
8	0	0	0	4
9	0	0	0	1
11	0	0	0	1
12	0	0	1	1
13	0	1	0	0
14	0	0	0	4
15	0	0	0	1
17	0	0	0	1
25	0	0	0	1
Total Relatives	*103*	*82*	*57*	*258*

Appendix Table 4a. Eigenvalues for parallel analyses of factors derived from Functioning items.

Factor Rank	**1**	**2**	**3**	**4**
Observed Eigenvalues	2.232	0.982	0.527	0.259
Eigenvalues from Uncorrelated Normal Variables	1.130	1.052	0.999	0.954

Appendix Table 4b. Eigenvalues for parallel analyses of factors derived from General Cognition tests.

Factor Rank	**1**	**2**	**3**	**4**
Observed Eigenvalues	4.615	0.893	0.751	0.584
Eigenvalues from Uncorrelated Normal Variables	1.247	1.158	1.107	1.065

Appendix Table 5a. One-tailed pairwise comparisons (using Fisher's r-to-z transformations) between diagnostic groups of the phenotypic correlations between General Cognition and Functioning.

	SC	MDD	SUD
MDD	0.65 (0.258)		
SUD	1.56 (0.059)	0.94 (0.174)	
ND	0.02 (0.492)	-0.75 (0.227)	-1.75* (0.040)

Appendix Table 5b. One-tailed pairwise comparisons (using Fisher's r-to-z transformations) between diagnostic groups of the phenotypic correlations between Emotion Perception and Functioning.

	SC	MDD	SUD
MDD	0.83 (0.203)		
SUD	0.26 (0.397)	-0.46 (0.323)	
ND	1.05 (0.147)	-0.02 (0.492)	0.53 (0.298)

Appendix Table 5c. One-tailed pairwise comparisons (using Fisher's r-to-z transformations) between diagnostic groups of the phenotypic correlations between Emotion Perception and Functioning after accounting for General Cognition.

	SC	MDD	SUD
MDD	-0.14 (0.444)		
SUD	-1.28 (0.100)	-1.15 (0.125)	
ND	0.35 (0.353)	0.51 (0.305)	1.77* (0.038)

Appendix Table 5d. One-tailed pairwise comparisons (using Fisher's r-to-z transformations) between diagnostic groups of the phenotypic correlations between Cognition and Emotion Perception.

	SC	MDD	SUD
MDD	3.13* (0.0001)		
SUD	0.25 (0.401)	-2.49* (0.006)	
ND	2.11* (0.017)	-1.74* (0.041)	1.45 (0.074)

* correlations differed significantly from each other at $p < 0.05$.

Appendix Table 6a. Phenotypic correlations among the General Cognition, Emotion Perception and Functioning items within the Schizophrenia group in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**0.335* (0.005)**	**0.133 (0.307)**	**0.342* (0.005)**	**-0.012 (0.924)**	**0.366* (0.003)**
Abstraction and Mental Flexibility	**0.387* (0.002)**	0.097 (0.470)	0.466* (0.0001)	-0.089 (0.438)	0.392* (0.003)
Attention	**0.373* (0.002)**	0.217 (0.105)	0.375* (0.002)	-0.014 (0.912)	0.225 (0.110)
Verbal Memory	**0.143 (0.262)**	0.065 (0.619)	0.124 (0.349)	0.047 (0.707)	0.205 (0.123)
Spatial Memory	**0.178 (0.185)**	0.117 (0.399)	0.192 (0.147)	0.044 (0.734)	0.301* (0.020)
Spatial Processing	**0.233 (0.091)**	0.096 (0.490)	0.247 (0.078)	-0.099 (0.432)	0.329* (0.015)
Sensorimotor Dexterity	**0.269* (0.029)**	0.111 (0.395)	0.279* (0.028)	-0.066 (0.606)	0.409* (0.002)
Trails A	**0.207 (0.091)**	-0.033 (0.806)	0.231 (0.060)	0.006 (0.965)	0.103 (0.431)
Trails B	**0.424* (0.0001)**	0.288* (0.026)	0.379* (0.003)	-0.025 (0.859)	0.308* (0.012)
California Verbal Learning Test	**0.384* (0.002)**	0.223 (0.086)	0.381* (0.003)	-0.047 (0.710)	0.437* (0.0001)
Emotion Perception Index	**0.301* (0.013)**	**0.163 (0.197)**	**0.298* (0.020)**	**0.078 (0.537)**	**0.285* (0.030)**
Facial Memory	**0.179 (0.147)**	0.067 (0.607)	0.167 (0.206)	0.004 (0.976)	0.224 (0.099)
Emotional Processing	**0.447* (0.001)**	0.219 (0.141)	0.378* (0.004)	0.066 (0.612)	0.287* (0.032)

Analyses conducted in SOLAR. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 6b. Phenotypic correlations among the General Cognition, Emotion Perception and Functioning items within the Major Depression group in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**0.245* (0.034)**	**0.171 (0.170)**	**0.245* (0.035)**	**0.179 (0.160)**	**0.312* (0.013)**
Abstraction and Mental Flexibility	**0.023 (0.855)**	0.072 (0.548)	-0.014 (0.913)	0.129 (0.297)	0.087 (0.527)
Attention	**0.149 (0.213)**	0.008 (0.953)	0.242* (0.049)	0.013 (0.912)	0.068 (0.600)
Verbal Memory	**0.127 (0.292)**	0.046 (0.710)	0.128 (0.278)	-0.003 (0.982)	0.070 (0.593)
Spatial Memory	**0.198 (0.121)**	0.225 (0.069)	0.172 (0.184)	0.102 (0.402)	0.209 (0.120)
Spatial Processing	**0.165 (0.151)**	0.054 (0.681)	0.200 (0.088)	0.126 (0.304)	0.183 (0.162)
Sensorimotor Dexterity	**0.227 (0.093)**	0.197 (0.151)	0.192 (0.147)	0.335* (0.008)	0.145 (0.285)
Trails A	**0.211 (0.063)**	0.176 (0.137)	0.194 (0.143)	0.072 (0.559)	0.274* (0.013)
Trails B	**0.083 (0.504)**	-0.067 (0.585)	0.113 (0.367)	0.147 (0.326)	0.181 (0.137)
California Verbal Learning Test	**0.329* (0.008)**	0.246* (0.049)	0.301* (0.015)	-0.049 (0.700)	0.308* (0.011)
Emotion Perception Index	**0.183 (0.114)**	**0.022 (0.866)**	**0.216 (0.066)**	**-0.010 (0.935)**	**0.061 (0.640)**
Facial Memory	**0.199 (0.108)**	0.128 (0.313)	0.218 (0.077)	0.024 (0.847)	0.174 (0.197)
Emotional Processing	**0.002 (0.989)**	-0.129 (0.255)	0.067 (0.573)	0.010 (0.933)	-0.016 (0.896)

Analyses conducted in SOLAR. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 6c. Phenotypic correlations among the General Cognition, Emotion Perception and Functioning items within the Substance abuse group in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**0.084 (0.542)**	**0.077 (0.577)**	**0.027 (0.849)**	**0.307* (0.022)**	**0.519* (0.0001)**
Abstraction and Mental Flexibility	**0.026 (0.855)**	-0.007 (0.960)	0.011 (0.941)	0.096 (0.341)	0.361* (0.025)
Attention	**0.338* (0.017)**	0.172 (0.217)	0.337* (0.017)	0.244 (0.074)	0.236 (0.133)
Verbal Memory	**0.111 (0.453)**	0.072 (0.606)	0.063 (0.668)	0.314* (0.018)	0.501* (0.001)
Spatial Memory	**0.153 (0.508)**	0.153 (0.276)	0.082 (0.572)	0.048 (0.730)	0.420* (0.007)
Spatial Processing	**-0.051 (0.728)**	-0.083 (0.565)	-0.090 (0.529)	0.257* (0.039)	0.479* (0.001)
Sensorimotor Dexterity	**0.110 (0.343)**	0.048 (0.755)	0.121 (0.428)	0.170 (0.215)	0.488* (0.001)
Trails A	**0.062 (0.664)**	0.154 (1.000)	0.037 (0.798)	0.098 (0.479)	0.244 (0.143)
Trails B	**-0.047 (0.728)**	0.070 (0.638)	-0.091 (0.541)	0.188 (0.139)	0.261 (0.124)
California Verbal Learning Test	**0.102 (0.485)**	0.215 (0.162)	0.023 (0.877)	0.240 (0.101)	0.381* (0.016)
Emotion Perception Index	**0.259 (0.072)**	**0.290* (0.035)**	**0.174 (0.221)**	**0.143 (0.490)**	**0.432* (0.003)**
Facial Memory	**0.154 (0.185)**	0.225 (0.136)	0.098 (0.498)	0.095 (0.497)	0.524* (0.001)
Emotional Processing	**0.263 (0.067)**	0.249 (0.073)	0.160 (0.141)	0.156 (0.325)	0.252 (0.100)

Analyses conducted in SOLAR. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 6d. Phenotypic correlations among the General Cognition, Emotion Perception and Functioning items within the No Diagnosis group in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**0.333* (0.0001)**	**0.262* (0.0001)**	**0.330* (0.0001)**	**0.221* (0.001)**	**0.232* (0.001)**
Abstraction and Mental Flexibility	**0.262* (0.0001)**	0.203* (0.002)	0.257* (0.0001)	0.201* (0.002)	0.113 (0.114)
Attention	**0.266* (0.0001)**	0.176* (0.011)	0.278* (0.0001)	0.074 (0.282)	0.239* (0.001)
Verbal Memory	**0.153* (0.022)**	0.087 (0.189)	0.140 (0.056)	0.222* (0.001)	0.233* (0.001)
Spatial Memory	**0.201* (0.003)**	0.188* (0.005)	0.185 (0.006)	0.106 (0.115)	0.138* (0.050)
Spatial Processing	**0.188* (0.006)**	0.132 (0.053)	0.173* (0.013)	0.278* (0.0001)	0.159* (0.021)
Sensorimotor Dexterity	**0.230* (0.001)**	0.170* (0.012)	0.225* (0.002)	0.102 (0.146)	0.116 (0.112)
Trails A	**0.230* (0.001)**	0.163* (0.015)	0.238* (0.0001)	0.025 (0.717)	0.086 (0.242)
Trails B	**0.231* (0.0001)**	0.190* (0.004)	0.233* (0.001)	0.140* (0.038)	0.236* (0.001)
California Verbal Learning Test	**-0.001 (0.987)**	0.021 (0.755)	-0.028 (0.690)	0.189* (0.007)	0.197* (0.010)
Emotion Perception Index	**0.185* (0.006)**	**0.163* (0.014)**	**0.149* (0.037)**	**0.218* (0.001)**	**0.165* (0.021)**
Facial Memory	**0.226* (0.001)**	0.184* (0.005)	0.203* (0.005)	0.136* (0.042)	0.152* (0.032)
Emotional Processing	**0.106 (0.118)**	0.101 (0.135)	0.080 (0.245)	0.240* (0.0001)	0.152* (0.037)

Analyses conducted in SOLAR. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 7a. Genetic correlations among the General Cognition, Emotion Perception and Functioning items within Schizophrenia in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**0.956* (0.0001)**	**0.564* (0.0001)**	**1.000* (0.0001)**	**0.700* (0.0001)**	**Not Computable**
Abstraction and Mental Flexibility	**1.000* (0.0001)**	0.650* (0.003)	0.929* (0.0001)	0.395* (0.0001)	0.720* (0.0001)
Attention	**1.000* (0.0001)**	1.000* (0.011)	1.000* (0.001)	1.000* (0.0001)	1.000* (0.0001)
Verbal Memory	**0.599* (0.025)**	0.335 (0.287)	0.690* (0.043)	0.533* (0.0001)	0.610* (0.0001)
Spatial Memory	**0.956* (0.014)**	0.552 (0.274)	0.997* (0.011)	0.996* (0.0001)	0.794* (0.0001)
Spatial Processing	**1.000* (0.002)**	0.856 (0.055)	1.000* (0.003)	0.760* (0.0001)	0.822* (0.0001)
Sensorimotor Dexterity	**0.899* (0.0001)**	0.560* (0.001)	0.895* (0.0001)	0.530* (0.0001)	0.499* (0.0001)
Trails A	**0.647* (0.016)**	0.341 (0.273)	0.746* (0.025)	0.501* (0.0001)	0.603* (0.0001)
Trails B	**1.000* (0.002)**	0.399 (0.272)	1.000* (0.002)	0.898* (0.0001)	0.927* (0.0001)
California Verbal Learning Test	**0.985* (0.023)**	0.386 (0.456)	1.000* (0.021)	0.829* (0.0001)	0.888* (0.0001)
Emotion Perception Index	**0.564* (0.016)**	**0.405 (0.196)**	**0.519 (0.056)**	**0.715* (0.0001)**	**0.771* (0.0001)**
Facial Memory	**0.460 (0.074)**	0.192 (0.559)	0.414 (0.173)	0.503* (0.0001)	0.542* (0.0001)
Emotional Processing	**0.916* (0.022)**	1.000* (0.041)	0.835* (0.049)	0.926* (0.0001)	1.000* (0.0001)

Analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 7b. Genetic correlations among the General Cognition, Emotion Perception and Functioning items within Major depression in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**1.000 (0.896)**	**-0.308 (0.586)**	**1.000 (0.606)**	**0.168 (0.819)**	**1.000 (0.113)**
Abstraction and Mental Flexibility	**1.000 (0.783)**	1.000 (0.459)	0.486 (1.000)	1.000 (0.550)	1.000 (0.293)
Attention	**1.000 (0.357)**	-0.009 (0.978)	1.000 (0.169)	0.154 (0.860)	0.753 (0.208)
Verbal Memory	**0.005 (1.000)**	-1.000 (0.479)	0.024 (1.000)	1.000 (0.614)	1.000 (0.260)
Spatial Memory	**0.299 (1.000)**	1.000 (0.531)	0.251 (0.999)	-1.000 (0.635)	-0.031 (0.985)
Spatial Processing	**-1.000 (0.921)**	-0.160 (0.722)	1.000 (0.902)	-0.020 (0.980)	1.000 (0.101)
Sensorimotor Dexterity	**-0.213 (0.664)**	0.072 (0.837)	-0.060 (0.932)	0.288 (0.548)	-0.102 (0.931)
Trails A	**-0.817 (1.000)**	-0.185 (0.661)	1.000 (0.935)	0.247 (0.645)	0.792* (0.001)
Trails B	**-1.000 (0.604)**	-1.000 (0.170)	0.165 (1.000)	-0.826 (0.325)	1.000 (0.406)
California Verbal Learning Test	**0.062 (1.000)**	-1.000 (0.532)	0.189 (1.000)	1.000 (0.559)	1.000 (0.745)
Emotion Perception Index	**-1.000 (0.756)**	**-0.819 (0.137)**	**1.000 (0.900)**	**-0.191 (0.860)**	**1.000 (0.181)**
Facial Memory	**1.000 (0.445)**	-0.054 (0.910)	1.000 (0.268)	-0.324 (0.696)	1.000 (0.314)
Emotional Processing	**-1.000 (0.280)**	-1.000* (0.027)	-1.000 (0.501)	-0.239 (0.840)	1.000 (0.206)

Analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 7c. Genetic correlations among the General Cognition, Emotion Perception and Functioning items within Substance abuse in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**1.000 (0.610)**	**0.046 (1.000)**	**1.000 (0.517)**	**1.000* (0.0001)**	**1.000 (0.526)**
Abstraction and Mental Flexibility	**1.000 (0.934)**	-1.000 (0.614)	1.000 (0.885)	0.324 (0.473)	1.000 (0.596)
Attention	**1.000 (0.594)**	1.000 (0.890)	1.000 (0.587)	1.000* (0.035)	1.000 (0.544)
Verbal Memory	**1.000 (0.610)**	-1.000 (0.716)	-0.016 (1.000)	1.000* (0.0001)	1.000 (0.905)
Spatial Memory	**0.029 (1.000)**	-0.269 (1.000)	-0.037 (1.000)	1.000 (0.056)	-0.017 (1.000)
Spatial Processing	**1.000 (0.429)**	-1.000 (0.820)	1.000 (0.207)	1.000* (0.0001)	1.000 (0.481)
Sensorimotor Dexterity	**1.000 (0.485)**	0.011 (1.000)	1.000 (0.376)	1.000* (0.001)	0.406 (0.845)
Trails A	**0.312 (1.000)**	0.034 (1.000)	0.060 (1.000)	1.000* (0.009)	0.051 (1.000)
Trails B	**0.138 (0.997)**	1.000 (0.327)	-0.640 (0.998)	0.581* (0.008)	-0.221 (1.000)
California Verbal Learning Test	**0.112 (1.000)**	0.038 (1.000)	0.179 (1.000)	1.000* (0.009)	0.095 (1.000)
Emotion Perception Index	**0.047 (1.000)**	**0.044 (1.000)**	**0.013 (1.000)**	**1.000* (0.001)**	**-0.041 (1.000)**
Facial Memory	**-0.051 (1.000)**	0.032 (1.000)	0.023 (1.000)	1.000 (0.071)	-0.003 (1.000)
Emotional Processing	**1.000 (0.720)**	-1.000 (0.657)	1.000 (0.553)	1.000* (0.010)	1.000 (0.843)

Analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 7d. Genetic correlations among the General Cognition, Emotion Perception and Functioning items within the No Diagnosis group in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**1.000 (0.852)**	**0.232 (0.764)**	**-1.000 (0.872)**	**0.469 (0.197)**	**0.398 (0.262)**
Abstraction and Mental Flexibility	**1.000 (0.406)**	1.000 (0.197)	1.000 (0.696)	0.760 (0.094)	-0.005 (0.992)
Attention	**1.000 (0.462)**	1.000 (0.170)	1.000 (0.855)	0.112 (0.739)	0.231 (0.411)
Verbal Memory	**-1.000 (0.379)**	-0.384 (0.581)	-1.000 (0.263)	0.380 (0.200)	0.378 (0.161)
Spatial Memory	**1.000 (0.204)**	1.000 (0.235)	1.000 (0.331)	0.184 (0.530)	-0.037 (0.879)
Spatial Processing	**1.000 (0.622)**	0.636 (0.569)	1.000 (0.606)	0.922* (0.039)	0.126 (0.782)
Sensorimotor Dexterity	**1.000 (0.465)**	1.000 (0.328)	1.000 (0.606)	0.405 (0.138)	0.223 (0.418)
Trails A	**0.737 (0.874)**	0.115 (0.866)	-1.000 (0.760)	0.244 (0.407)	0.328 (0.212)
Trails B	**0.487 (1.000)**	1.000 (0.484)	0.295 (1.000)	1.000 (0.470)	1.000 (0.526)
California Verbal Learning Test	**-1.000 (0.497)**	-0.338 (0.590)	-1.000 (0.520)	0.637* (0.034)	0.248 (0.265)
Emotion Perception Index	**-1.000 (0.677)**	**-0.279 (0.599)**	**-1.000 (0.507)**	**0.496 (0.070)**	**0.347 (0.108)**
Facial Memory	**-1.000 (0.492)**	-0.344 (0.574)	-1.000 (0.329)	0.396 (0.210)	0.253 (0.372)
Emotional Processing	**1.000 (0.913)**	-0.152 (0.814)	-1.000 (0.841)	0.555 (0.082)	0.392 (0.070)

Analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 8a. Environmental correlations among the General Cognition, Emotion Perception and Functioning items within Schizophrenia in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**-1.000 (0.072)**	**-1.000 (0.292)**	**-1.000 (0.098)**	**-1.000 (0.170)**	**Not Computable**
Abstraction and Mental Flexibility	**-1.000 (0.183)**	-1.000 (0.304)	-1.000 (0.608)	-1.000 (0.727)	-1.000 (0.262)
Attention	**-0.498 (0.217)**	-0.399 (0.218)	-0.390 (0.288)	-1.000* (0.034)	-1.000* (0.014)
Verbal Memory	**-0.511 (0.329)**	-0.148 (0.750)	-0.500 (0.267)	-1.000 (0.569)	-1.000 (0.494)
Spatial Memory	**-0.446 (0.284)**	-0.094 (0.803)	-0.493 (0.217)	-1.000 (0.112)	-1.000 (0.662)
Spatial Processing	**-0.639 (0.135)**	-0.430 (0.262)	-0.655 (0.143)	-1.000 (0.289)	-1.000 (0.393)
Sensorimotor Dexterity	**-1.000* (0.013)**	-1.000 (0.087)	-1.000* (0.022)	-1.000 (0.385)	-1.000 (0.905)
Trails A	**-0.457 (0.366)**	-0.263 (0.591)	-0.388 (0.394)	-1.000 (0.556)	-1.000 (0.399)
Trails B	**-0.320 (0.402)**	0.006 (0.989)	-0.438 (0.292)	-1.000 (0.337)	-1.000 (0.180)
California Verbal Learning Test	**-0.024 (0.933)**	0.102 (0.711)	-0.034 (0.898)	-0.903 (0.410)	-1.000 (0.938)
Emotion Perception Index	**-0.364 (0.649)**	**-0.144 (0.837)**	**-0.137 (0.861)**	**-1.000 (0.223)**	**-1.000 (0.213)**
Facial Memory	**-0.336 (0.622)**	0.095 (0.858)	-0.156 (0.778)	-1.000 (0.516)	-1.000 (0.658)
Emotional Processing	**-0.096 (0.818)**	-0.391 (0.377)	-0.006 (0.989)	-1.000 (0.096)	-1.000 (0.131)

Analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 8b. Environmental correlations among the General Cognition, Emotion Perception and Functioning items within Major depression in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**0.179 (0.610)**	**0.562 (0.323)**	**0.043 (0.887)**	**0.233 (0.689)**	**-0.395 (0.434)**
Abstraction and Mental Flexibility	**0.036 (0.903)**	-0.248 (0.696)	0.080 (1.000)	-0.107 (0.768)	-0.187 (0.629)
Attention	**-0.165 (0.660)**	0.647 (0.642)	-0.244 (0.458)	-0.136 (0.798)	-0.748 (0.227)
Verbal Memory	**0.004 (0.966)**	0.264 (0.513)	0.003 (0.977)	-0.055 (0.841)	-0.208 (0.465)
Spatial Memory	**0.131 (0.787)**	-0.074 (0.866)	0.104 (0.763)	0.375 (0.126)	0.177 (0.662)
Spatial Processing	**0.246 (0.178)**	0.361 (0.615)	0.191 (0.648)	0.381 (0.559)	-0.550 (0.203)
Sensorimotor Dexterity	**0.899 (0.257)**	1.000 (0.347)	0.358 (0.577)	-0.229 (0.928)	0.347 (0.610)
Trails A	**0.751 (0.061)**	1.000 (0.379)	1.000 (0.691)	-0.551 (0.904)	-1.000 (0.688)
Trails B	**0.306 (0.122)**	0.651 (0.163)	0.179 (0.548)	0.938* (0.018)	-0.043 (0.886)
California Verbal Learning Test	**0.204* (0.028)**	0.586* (0.039)	0.190 (0.248)	-0.156 (0.682)	0.218 (0.516)
Emotion Perception Index	**0.241 (0.168)**	**0.969* (0.039)**	**0.092 (0.705)**	**0.180 (0.766)**	**-0.353 (0.297)**
Facial Memory	**-0.040 (0.920)**	0.387 (0.583)	-0.135 (0.719)	0.376 (0.666)	-0.218 (0.619)
Emotional Processing	**0.480 (0.278)**	1.000* (0.035)	0.220 (0.404)	0.192 (0.753)	-0.417 (0.214)

Analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 8c. Environmental correlations among the General Cognition, Emotion Perception and Functioning items within Substance abuse in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**-0.042 (0.847)**	**0.019 (0.876)**	**-0.115 (0.611)**	**-1.000 (0.105)**	**0.087 (0.788)**
Abstraction and Mental Flexibility	**0.115 (0.792)**	0.309 (0.379)	0.054 (0.899)	-0.762 (0.688)	0.130 (0.665)
Attention	**0.051 (0.841)**	0.136 (0.632)	0.008 (0.976)	-1.000 (0.118)	-0.201 (0.536)
Verbal Memory	**-0.158 (0.463)**	0.046 (0.860)	-0.096 (0.478)	-1.000 (0.067)	0.133 (0.734)
Spatial Memory	**0.064 (0.422)**	0.037 (0.643)	0.045 (0.574)	-1.000 (0.281)	0.178* (0.047)
Spatial Processing	**-0.225 (0.372)**	-0.043 (0.845)	-0.379 (0.198)	-1.000 (0.110)	0.028 (0.940)
Sensorimotor Dexterity	**-0.120 (0.745)**	0.095 (0.724)	-0.219 (0.554)	-1.000 (0.110)	0.342 (0.539)
Trails A	**0.056 (0.526)**	0.024 (0.787)	0.027 (0.762)	-1.000 (0.613)	0.204* (0.043)
Trails B	**0.080 (0.888)**	-0.932 (0.531)	0.077 (0.723)	-1.000 (0.361)	0.129 (0.383)
California Verbal Learning Test	**0.031 (0.744)**	0.054 (0.595)	-0.002 (0.983)	-0.996 (0.783)	0.156 (0.326)
Emotion Perception Index	**0.102 (0.498)**	**0.161 (0.377)**	**0.050 (0.931)**	**-1.000 (0.135)**	**0.194 (0.087)**
Facial Memory	**0.084 (0.343)**	0.106 (0.232)	0.026 (0.773)	-1.000 (0.271)	0.241* (0.019)
Emotional Processing	**0.033 (0.898)**	0.248 (0.173)	-0.076 (0.781)	-1.000 (0.111)	0.033 (0.947)

Analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 8d. Environmental correlations among the General Cognition, Emotion Perception and Functioning items within the No Diagnosis group in the pedigree sample.

	Functioning Index	Marital Status	Living Situation	Current Occupation	Global Functioning
General Cognition Index	**0.269*** **(0.005)**	**0.192** **(0.082)**	**0.288*** **(0.0001)**	**0.153** **(0.249)**	**0.054** **(0.700)**
Abstraction and Mental Flexibility	**0.166** **(0.084)**	0.070 (0.471)	0.191* (0.042)	-0.009 (0.952)	0.123 (0.395)
Attention	**0.164** **(0.155)**	0.018 (0.880)	0.232* (0.047)	0.030 (0.850)	0.089 (0.589)
Verbal Memory	**0.196** **(0.063)**	0.117 (0.232)	0.191 (0.100)	0.105 (0.553)	-0.037 (0.831)
Spatial Memory	**0.065** **(0.555)**	0.015 (0.898)	0.095 (0.392)	0.077 (0.637)	0.160 (0.345)
Spatial Processing	**0.105** **(0.278)**	0.022 (0.850)	0.148 (0.170)	0.096 (0.478)	0.091 (0.534)
Sensorimotor Dexterity	**0.143** **(0.184)**	0.065 (0.568)	0.148 (0.170)	0.007 (0.963)	0.005 (0.977)
Trails A	**0.202** **(0.069)**	0.132 (0.274)	0.250* (0.001)	-0.013 (0.931)	-0.070 (0.668)
Trails B	**0.163** **(0.061)**	0.101 (0.250)	0.201* (0.030)	0.090 (0.489)	0.144 (0.271)
California Verbal Learning Test	**0.104** **(0.491)**	0.101 (0.558)	0.072 (0.625)	-0.144 (0.492)	0.083 (0.691)
Emotion Perception Index	**0.244*** **(0.008)**	**0.248** **(0.089)**	**0.229*** **(0.033)**	**0.017** **(0.924)**	**-0.136** **(0.477)**
Facial Memory	**0.281*** **(0.001)**	0.241 (0.056)	0.269* (0.006)	0.003 (0.984)	0.063 (0.691)
Emotional Processing	**0.074** **(0.569)**	0.120 (0.395)	0.085 (0.362)	0.034 (0.837)	-0.262 (0.192)

Analyses conducted in SOLAR including Controls. Covariates include age and sex, with p-values indicated in parentheses. *$p < 0.05$ (two-tailed)

Appendix Table 9. Summary of mean group comparisons, heritabilities, and phenotypic, genetic and environmental correlations with functioning for general cognition after covarying Emotion Perception.

		SC	MDD	SUD	ND	Controls
General Cognition$^{\lozenge}$	**Mean (SD)**	-0.901 [a] (1.318)	0.115 [b] (0.831)*	-0.035 [b] (0.694)*	0.191 [b] (0.836)*	0.149 [b] (0.870)*
	Heritability	1.000* (0.0001)	0.705 (0.064)	0.576 (0.142)	0.274* (0.014)	
General Cognition$^{\lozenge}$**/ Functioning**	R_P	0.141 (0.215)	0.202 (0.079)	-0.143 (0.306)	0.264* (0.0001)	0.059 (0.600)
	R_G	0.843* (0.0001)	1.000 (0.862)	1.000 (0.313)	1.000 (0.221)	
	R_E	-1.000* (0.043)	0.250 (0.071)	-0.525 (0.300)	0.128 (0.237)	
General Cognition/ Emotion Perception	R_P	0.777* (0.0001)	0.491* (0.0001)	0.758* (0.0001)	0.644* (0.0001)	0.433* (0.0001)
	R_G	0.736* (0.002)	0.808 (0.307)	0.803 (1.000)	0.695* (0.033)	
	R_E	1.000 (0.583)	0.244 (0.656)	0.700 (1.000)	0.620* (0.0001)	

Given that all omnibus tests of group means were significant at $p = 0.0001$, post-hoc Tukey's pairwise tests were conducted. Statistics sharing the same superscripts did not differ significantly ($p \leq 0.05$) from each other (i.e. were included in a homogeneous subset). Mean group comparisons ($F(4,189)=12.46$, $p = 0.0001$) include standard deviations in parentheses, while heritabilities and correlations include p-values in parentheses. Covariates include age and sex. *$p < 0.05$ (two-tailed). $^{\lozenge}$additional covariate: Emotion Perception

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